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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

NOVEMBER, 1949

ORIGINAL ARTICLES

BLOOD TEMPERATURE AND ITS CONTROL*

By H. C. Bazett, M.D.
PHILADELPHIA, PENNSYLVANIA

(From the Department of Physiology, Medical School, University of Pennsylvania)

Blood temperature is a term often used loosely, in which blood temperature is confused with body temperature. Blood temperature is usually thought to be regulated at some constant level. It is in no way constant. It shows great fluctuations from time to time and from place to place, and controlled fluctuations in peripheral vessels are utilized to regulate the temperature in the central vessels at a more or less constant level. The blood acts as a common carrier of heat from one area to another, a function which is incompatible with a constant thermal load. The regulation of this circulatory function appears to depend on at least 3 mechanisms: the direct reaction of blood vessels to temperature levels; reflex responses to thermal sensations; and the reactions of two reciprocal centers in the hypothalmus to the temperature levels to which they are exposed, through which the temperature of the blood supplying them is regulated. Malfunction of the whole mechanism is commonly attributed to simple failure of these higher centers; such a limited point of view is apt to be inaccurate, and should not be adopted even tentatively.

The inconstancy of blood temperature, and its function as a regulating, rather than a regulated, factor, has been known since the days of Claude Bernard, who himself described it. However, the magnitude of these variations generally has not been recognized. Modern catheterization, with the use of non-wetting plastics, allows thermocouples to be left in place for hours, so that much more definite information has become available. Figure 1 illustrates such a thermocouple encased in a plastic tube of less than 0.5 mm. diameter and inserted 4.5 cm. up the brachial artery. It is quite easy to insert such catheters for 20 cm. or more and to reach the abdominal aorta or vena cava from the femoral region, or to travel along other similar vessels.

The variability of the *venous temperature* has been generally accepted, as has that of capillary blood. It is inconceivable that large temperature differences could exist between the blood in such vessels and the tissues, separated as they are by such thin membranes.

* The fourteenth Hughlings Jackson lecture delivered at the Montreal Neurological Institute, McGill University, Montreal, on May 13, 1949, reviewing recent work supported by a Life Insurance Medical Research Fund Grant.

On the other hand, *arterial temperature*, with blood flowing rapidly to the periphery, is usually supposed to be relatively constant. Actual measurements[8] show such a conclusion to be quite erroneous except in a very warm environment. Thus temperatures have been observed as low as 21.5° C in the radial artery in a room at 9° to 10.5° C, 25.1° in the dorsalis pedis in a room at 20°, and 31.1° in the brachial artery in a room at 13.3°. In the last case the low temperature was due in part to immersion of the limb distal to the point of measurement for short periods in cold water. That the environmental temperature affects the thermal gradients between the brachial and radial arteries, as well as their levels, is shown in Figure 2. This figure also indicates that arterial temperatures may be modified very readily by exposure of the limb to local cooling (or warming) considerably distal to the point of measurement.

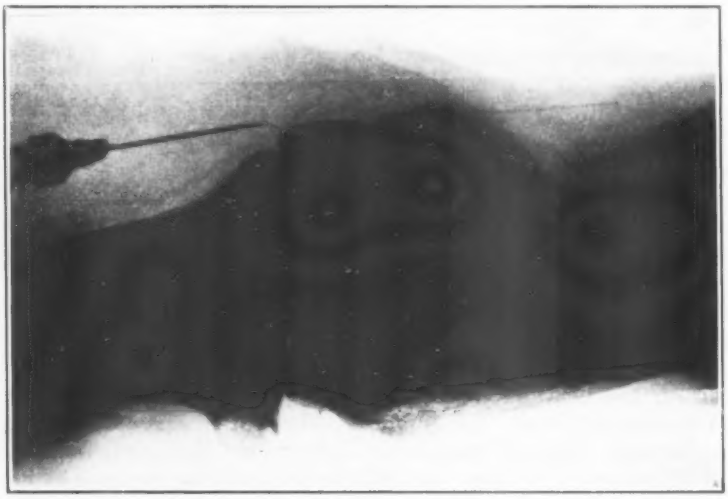

FIG. 1. Roentgenogram of plastic covered thermocouple introduced into the brachial artery.

Cooling of blood flowing in an artery of the degree indicated implies a large exchange of heat, yet surfaces of overlying arteries are not detectably warmed. The close association of veins with peripheral arteries explains these anomalies, since the heat lost by the arteries should reheat the cooled blood in the veins. The falling gradients of temperature in the arteries are matched by rising gradients in the returning venous blood. Light compression of these veins below a point of measurement of arterial temperature interferes with their cooling effect on the artery above it and can cause a marked rise of arterial temperature. The exchange of heat between artery and vein has also been demonstrated in animal experiments by Dr. Leon Eisenberg[12] by the perfusion of cool saline into a vein. No extensive proof of this heat exchange is needed, since the known anatomical relationships of peripheral arteries with venae comites renders the existence of such exchange inevitable. Indeed this exchange appears to be the main function of the arrangement. It is surprising that its importance was not recognized earlier on mere theoretical grounds.

Other evidence of the large heat exchange exists. In a cool environment

the thermal gradient across the thin arterial wall is of the order of 1 to 2° C, which in itself indicates a large heat flow, since the insulation must be low. Also under conditions of rapid cooling particularly in readjustments to new conditions, large pulsatile changes in temperature within the arteries often may be seen, indicating that the system is reacting as a natural "thermostromuhr". Pressure pulsations cause pulsatile changes in blood flow and these in turn pulse-like changes in arterial temperature.

Examples of such pulsatile changes are shown in Figure 3. In the topmost record there was only a small thermal gradient between the brachial and radial (see graph for room conditions at 22° C of Figure 2), though a steeper gradient appeared to exist more distally along the radial artery. Only slight "pulsations" in temperature are visible in the radial, while in the brachial only those accompanying extra systoles were readily detected. Three hours later the middle record was obtained when the arm had been recovering for 5 minutes after a 10 minute immersion of the hand alone (below both couples) in water at 2° C. At the signal on this record the hand and lower forearm were immersed in water at 2° C. The earlier cooling and rewarming had exaggerated the thermal gradients along the vessel and had increased pulsations. The second cooling temporarily decreased the pulsatile changes in the radial and caused a rise in brachial temperature, as vasoconstriction reduced the venous return. At the end of 5 minutes just before the signal in

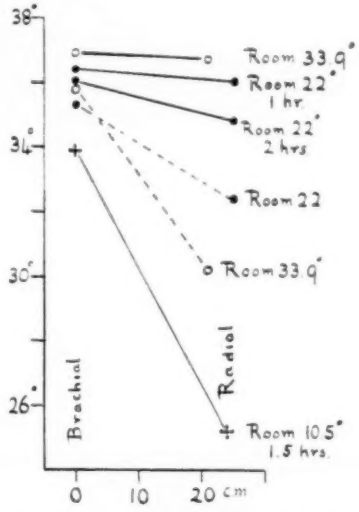

FIG. 2. Thermal gradients observed in a single subject between the brachial and radial arteries at different room temperatures (as indicated.) Values obtained in room temperatures of 33.9° and 22° C, which are connected with dotted lines, were obtained when the distal part of the limb had been cooled by immersion in cold water. In the former case this immersion was as stated previously and published[8] (Exp. 11 of that series), while that at 22° was as stated for records reproduced in Fig. 3. In both cases all or most of the cooling was applied distal to the thermocouples.

In the experiment in the room at 22° C, another couple had been inserted in the radial artery on the back of the hand close to the origin of the artery to the thumb. The temperature gradient in the 4 to 6 cm. length between the two couples in the radial appeared to be of the order of 4°.

the lowermost record, both radial and brachial temperatures had fallen, and the pulsations in the radial had regained their size, as the greater cooling of venous blood compensated for the slower rate of flow. The gradient shown in Figure 2 as occurring after cooling in a room at 22° is that recorded here. After the signal when the hand and forearm were immersed in water at 18° C, the increase in temperature produced a sensation of warmth with vasodilatation (in spite of its low level) and the temporary rapid flow of very cold venous blood associated with a rapidly inflowing arterial stream gave greatly exaggerated pulsations.

Gravity can induce similar effects, as is illustrated by Fig. 4. An individual, who was somewhat cool and was lying in a semi-inclined position, held his arm horizontal at shoulder level, and then lowered it to his side at the time indicated by the signal. There

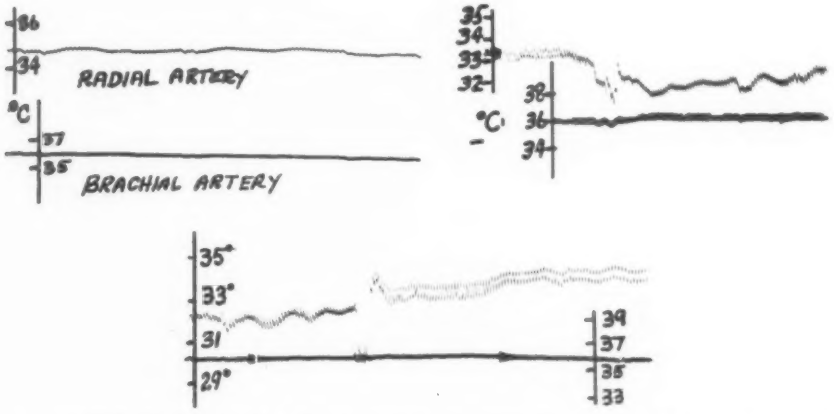

FIG. 3. Records of radial and brachial arterial temperatures measured in a room at 22° C (72° F.) after exposure for 3 hours. The left upper record represents conditions after some earlier moderate cooling of the hand (distal to the couples) in water. The right upper record was obtained after the hand had been immersed for 10 minutes in water at 2° C and had been allowed to rewarm in air for 5 minutes. At the signal the hand, and on this occasion also the forearm, were immersed in water at 2° for 5 minutes. The whole section reproduced before and after immersion represents 100 secs., which indicates the time scale for all these records. The lowest record shows the end of this 5 minute immersion, which was followed at the time of the signal by transfer to water at 18° C.

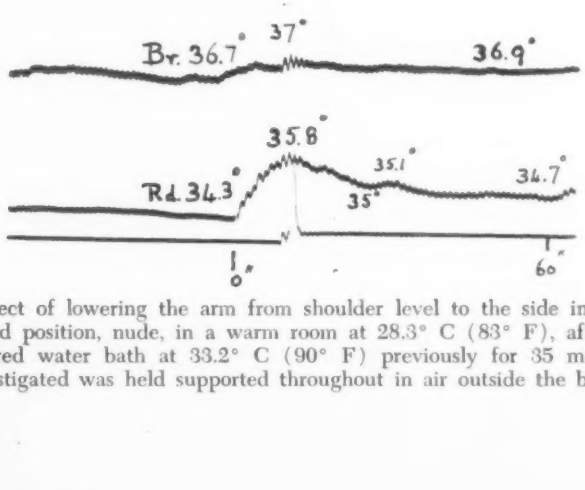

FIG. 4. The effect of lowering the arm from shoulder level to the side in a subject lying in a semi-inclined position, nude, in a warm room at 28.3° C (83° F), after he had been cooled in a stirred water bath at 33.2° C (90° F) previously for 35 minutes. The arm investigated was held supported throughout in air outside the bath.

resulted increases in temperature in both brachial and radial arteries, while the pulsatile changes in temperature originally visible in the brachial artery were reduced and those of the radial increased. Gravity effects presumably temporarily slowed venous flow in the veins adjacent to the brachial, so that heat exchange in this area was reduced. On the other hand, the resulting engorgement of the more peripheral veins exaggerated cooling of the blood in the radial. The exchange of heat between the arteries and veins was shifted to a more peripheral position. Yet the considerable thermal changes were not accompanied by any conscious sensation of temperature.

The changes described depend on circulatory adjustments through which cool blood returning in venae comites causes *precooling of entering arterial blood.* This allows an internal exchange of heat with supply of oxygen to the peripheral tissues and economy of heat loss. Attainment of a steady state seems compatible with considerable thermal gradients along the arteries, as well as along the axes of the limbs. On the other hand under such conditions gradients between the vessels and tissues are probably relatively small. Thus in warm rooms averaging some 26° C (79° F) Pennes[21] found brachial temperatures averaging 0.96° C below those of the rectum, while the deep tissues of the forearm had temperatures only 0.16° below that of the brachial. The longitudinal gradient in aggregate was considerable, the transverse relatively slight.

A mechanism through which precooling of arterial blood is brought about should be a considerable disadvantage in a warm environment. In such an environment it appears actually to be absent, for the temperatures observed on the surfaces of the tips of the fingers or toes may exceed those observed on more central surfaces[16]. The return of venous blood through superficial veins, far removed from the arteries, which is so well recognized, would explain this adjustment, though this might be more effective if dilatation of superficial veins was associated with reciprocal constriction of the deeper channels. Reports have been made of experimental evidence of such reciprocal vascular reactions, possibly involving veins, present as a peripheral mechanism, even in the absence of all true reflexes. Such a type of control is surprising.

Direct Reactions of Vessels. J. R. Pappenheimer *et al.*[20] have described constriction of superficial cutaneous vessels and a reciprocal dilation of deep vessels when excised limbs are perfused with cooled blood. The condition is reversed when the blood is warmed. Also Perkins *et al.*[22] have demonstrated vasoconstrictor responses in the skin of dogs in areas which have been sympathectomized or denervated, if the skin surface falls below 22° C. In these cases the vasoconstriction appears to be due to direct effects on the vessels, rather than on axone reflexes. In all probability similar responses can develop in normal innervated skin in man, even though they are not always obvious. Thus exposure of hands to extreme cold has been repeatedly described as giving rise to severe pain, starting at a critical level of skin temperature of about 10° C, as in experiments testing gloves during the war period. The same temperature is regarded as a critical one by Aschoff[1] in experiments with hand baths, as vasodilator reactions commonly develop at temperatures below this level. This is also considered by Ungley[27] as a critical level for the development of immersion foot. In our experiments[9] pain has developed at or about these levels and this pain has often been preceded by an abrupt fall of temperature, suggesting vascular spasm. Dilator reactions often

have followed the pain, and have appeared to be inflammatory in character and of the axone reflex type described by Lewis[15]. In such reactions the temperature of a surface exposed to cold may be increased through 10° to 15° C in as many minutes. It seems improbable that this could happen, unless the venous return is directed up superficial veins (and away from the venae comites) also under such conditions.

Reflex responses to thermal sensations provide the mechanisms through which rapid reactions to sudden changes are attained. The existence of reflex vasoconstriction to cold is fully established. The reaction is relatively simple in that superficial vasoconstriction allows surface temperatures to fall, and thermal conductance is reduced. In consequence central temperatures in the trunk, and in the large arteries leaving the trunk, rise, as cooling by returning venous blood is reduced. Cooling effects are observed rapidly, and extend to peripheral areas not exposed to the cooling even if the blood supply of the cooled area has been occluded[23].

Reflex responses to warmth are less definite and their existence has been denied[23]. Effects on distant areas are delayed for minutes. Occlusion of the vessels of the warmed area is usually claimed[23], but not always[10], to prevent any such general effects. The existence of reflex responses to warmth on the other hand has been claimed on the basis of vasodilatation accompanying a fall of rectal temperature[17]. Such evidence is not reliable, for, as will be seen later, rectal temperature is a poor index of hypothalamic changes. The discordant statements depend on failure to allow for the complexities imposed by vasodilatation. During such reactions in rewarming thermal conductance is increased and heat is distributed more evenly through the body, so that some areas are warmed at the expense of others. Rises in temperature are strictly local, and usually are seen first in the cooler more peripheral areas[24]. Not only is the outflow of warm arterial blood accelerated but also the return flow of cooled venous blood. Consequently, the temperature of the blood in any given artery may at first either rise or fall, or vasodilatation may be evidenced by increased pulsatile changes in temperature without any alteration in the mean level. The utilization of a background of cooled skin, on which the effects may be demonstrated, may have contributed to the apparent long delays, since reflex vasodilatation probably cannot readily overcome a spasm due to direct cooling of the vessel.

The apparent prevention of general effects by the mere occlusion of the vessels of the warmed area is not surprising, for warming is an active process, not a passive one as is cooling. If the inflow of heat is prevented, any vasodilatation is apt to be evanescent. The increased thermal conductance speeds heat loss and the reaction therefore may be self-limiting.

The existence of reflex vasodilatation to warmth can be readily demonstrated by vascular temperatures, for an increase in arterial temperature in a properly chosen vessel may be demonstrated in a distant area with a latency of only 10 seconds, which entirely excludes any direct effect of temperature changes on the centers (unpublished data). The complexities are well demonstrated by the facts that rewarming of a hand after previous pronounced cooling can cause dilatation which shows itself by a sudden precipitous fall in brachial arterial temperature[8]. Similarly a rewarming of a cooled hand may cause a precipitous fall in temperature on the palmar surface[9]. Thus both increases and decreases in surface temperature may

indicate increased thermal conductance produced by vasodilatation, and the areas most favorable for demonstrating the increases are not always easy to predict.

Thermal sensations which give rise to vasoconstrictor or vasodilator reflexes are not dependent on the temperature levels in the skin. The well known phenomena of adaptation exclude such an hypothesis. Nor can they be explained as due to the rate and direction of change. If an arm be immersed in water warm enough to maintain the surface at a temperature significantly above that of arterial blood entering the arm, sensations of warmth continue indefinitely, even though a steady state is maintained. On the other hand lowering the temperature of such a bath for instance from 40° to 39° may give a temporary absence of warmth[13]. However, this sensation returns after the tissues just below the skin have had time to cool, and then again continues indefinitely. Thus the evidence indicates that the sensation arises as the result of the thermal gradients which are set up, and disappears as these are temporarily extinguished.

In order to obtain experimental reversal of these gradients Dr. McGlone and I many years ago investigated the thermal sensations generated in a double fold of prepuce where a recognizable thermal receptor could be stimulated from either side of the fold[4,5]. Normal sensations were generated from both sides, though the intensities of the sensations and their latencies varied. A simple gradient is inadequate to explain the phenomena, and it seems probable that the special arrangement of the vessels in the dermis described by Spalteholz[25] is concerned, as indeed he surmised[26]. Theories built on this basis have been discussed earlier[7]. Here it is only necessary to state that thermal gradients observed in relatively thick skin demonstrate that this anatomical arrangement does affect heat distribution. It would appear that cold sensations are caused by alterations in the gradients superficial to the arteriolar plexus, and warm sensations by those just deep to it, where the deeper tissues are normally cooler than those more superficial. On such hypotheses the marked changes in arterial temperature that can occur in the larger and more central vessels should have little effect on the sensory mechanisms. This appears to be the case.

There remains a possibility that deep receptors of temperature exist, even though there is no obvious conscious sensation. If so, it is unlikely that receptors are situated in or near the vessels, for large exchanges of heat, such as those indicated in Figure 4, give no indication of having induced either sensations or reactions. In the prepuce sensory receptors for warmth can be identified as existing in the subcutaneous as well as in dermal layers. Deep receptors might also occur in the subcutaneous tissues beneath the thicker skin of other parts of the body where probably they would not be recognizable as sensitive spots. While cold is purely an exteroceptive sensation, warmth can be either exteroceptive or proprioceptive, since heat may be generated in muscles. Deeper receptors might be concerned with heat of such internal origin. Even here gradients in temperature would probably act as the stimulus, since warming of deeper tissues by focused micro-wave radiation does not induce sensations of warmth[14].

Sensations of temperature may be modified by various factors. Thus dilatation of the dermal vessels, however produced, not only modifies the thermal gradients in the skin, but also lowers the sensitivity to cold in spite of the raised surface temperature. Thus both

the threshold for stimulation and the latency of sensation are increased[3,4]. These observations have been confirmed and established firmly by Ebaugh and Thauer[11], who, however, were unable to confirm any facilitation of sensations of warmth ascribed to vasodilatation on more slender evidence[3]. On the other hand vasodilatation does not appear to increase the latency for warmth as it does for cold[4]. Vasodilatation may cause increased heat capacity, and more rapid thermal conduction; conditions are complex. Sensations are also modified by carbon dioxide in a way which may be dependent on the vascular reactions. Thus water baths charged with carbon dioxide do not feel as cold as do normal baths at the same temperature. Inspiration of carbon dioxide may also cause a wave of sensation of warmth, which is attributed in consciousness to dermal tissues. Heat directly conducted to the subcutaneous tissues from the muscles either by veins or arteries may be responsible for sensations of warmth which accompany exercise. These are usually associated with the occurrence of sweating in the limbs during work, even if the individual is exposed to an extremely cold environment.

No emphasis need be placed here on the well recognized characteristics of spatial summation and adaptation that are found in thermal sensations. It should be noted, however, that adaptation in this case does not appear to be a property of the receptors, so much as one of the accessory mechanisms of the stimulus. Thermal sensations fade when the thermal gradients are reduced, as the thermal changes spread more deeply. They persist indefinitely, if the circulation of blood at normal temperature to a locally heated area maintains an adequate gradient. Adaptation is more pronounced with cold stimuli, since the slowed blood flow which accompanies vasoconstriction, is unable to maintain the thermal gradients. Thermal stimuli may, therefore, be compared with those of light. This causes adaptation in the eye by bleaching rhodopsin, thus also affecting an accessory rather than a receptor mechanism. It would, however, be rash to generalize and apply such conclusions to other receptors, for each receptor appears to be adjusted to its own function and many different mechanisms may be utilized.

Sensory receptors for temperature appear to be stimulated also by other forms of stimulus, for release of vascular stasis may generate intense sensations unassociated with measurable thermal changes[6]. Possibly osmotic or chemical stimuli are involved.

Regulation of hypothalamic temperature by the blood stream appears to be attained by the adjustment of the temperature of the inflowing blood supplying these tissues. Several measurements of the temperature within the right internal jugular bulb have been made in man, and this temperature has usually been found some 0.2° above that simultaneously observed in external iliac arteries. In view of the high metabolism of the brain this is not surprising. In one experiment a thermocouple was left in place for hours in this vessel, so that its temperature could be compared with those observed in the rectum, external iliac, femoral and dorsalis pedis arteries, and with that at the distal end of the inferior vena cava. The individual was inadequately clothed below the waist, and was lying in a room at 20° C (68° F), so that cooling occurred, while the heat loss was mainly from the lower limbs. After several hours of such cooling the subject was rewarmed by immersion of both hands and forearms in hot water, so that rewarming depended on heat acceptance by the upper limbs.

Comparison of the internal jugular temperature with that of the rectum

after about one hour's exposure showed identical temperatures, probably due to a more rapid cooling of the jugular bulb. Later the rectal temperature always remained the lower, when the delay in its cooling had been overcome. The hypothalamic temperature variations were of the same order of magnitude as those of the rectum but occurred much more abruptly, since they were less damped by large heat capacity effects. Owing to these differences in the time characteristics, differences as great as 1.4° C (2.5° F) were set up (in favor of the jugular bulb over the rectum) during warming, and reduced to 0.6° C (1.1° F) on recooling. The latter difference increased again to over 1° C as the cooling effects approached more nearly to a steady state. The temperature of the jugular bulb, which probably reflects that of the hypothalamus, is therefore by no means steady but swings more readily and more rapidly than does that of the rectum. It may not be entirely protected from local influences since drinking two cups of hot tea raised the temperature of the jugular bulb by 0.5° C in 5 minutes, while the temperature in the external iliac artery, inferior vena cava and rectum were much less affected. While the hypothalamic temperature may be regulated, it is by no means free of fluctuations.

The regulation of fluctuations in temperature in peripheral vessels are such as to induce smaller changes in the temperatures of central vessels, such as would tend to return the hypothalamic temperature to its normal level. These temperatures in the larger arteries are similar to those found in the jugular bulb, though their levels are somewhat lower. Like the fluctuations of the jugular bulb, they occur more readily and more abruptly than do fluctuations in the rectum. The temperatures existing in these central arteries induce relatively constant and similar levels of temperature in the central areas of the body, namely the thorax, abdomen and cranium. Thus central body temperature is controlled. However, these central temperature levels are not precisely identical under conditions of asymmetrical cooling, such as that used in this experiment. Here the temperature in the external iliac artery and inferior vena cava commonly were 0.1° to 1.1° above that of the rectum, while the temperature of the femoral artery just below Poupart's ligament might be 0.8° above or below that of the rectum. Considerable effects of local warming and cooling were in evidence in both the external iliac and femoral arteries, and to a small degree in the inferior vena cava.

One could probably accept temperatures in the abdominal aorta at the level of its bifurcation as representing approximately central arterial temperature. This is a point readily reached with thermocouples. Distal to this, steep thermal gradients may develop. Thus at the end of this experiment a gradient of 1° C was to be found in the iliac vein in a distance of 4 cm. (between points 6.5 cm. and some 2.5 cm. above Poupart's ligament). Deep rectal temperature is probably closely related to temperatures observable in the iliac arteries and veins just central to Poupart's ligament; it does not represent a true central temperature unaffected by local changes.

Summary. One may conclude that current theories of thermal control are not grossly in error, even though the evidence on which they are founded, is by no means reliable. A theory, such as that advanced years ago by Meyer[18], supposing the existence of two opposing centers, one in the anterior hypothalamus controlling heat dissipation and one lying more posteriorly controlling heat conservation, still seems adequate. Presumably the former center is stimulated by sensations of

warmth and has an optimal temperature for activity, which lies above the normal hypothalamic temperature, while the latter is stimulated by sensations of cold and has an optimal temperature below the normal level. The combination of reactions initiated either reflexly or centrally through these centers is reinforced and maintained also by local reactions of the cutaneous and deeper blood vessels themselves to temperature levels, as far as the vascular components of the reaction are concerned.

Such an hypothesis, however, fails to account for regulation of central body temperature at higher levels during exercise, as described by Nielsen[19]. Such levels vary with the metabolic loads imposed by the work and appear to induce higher temperatures for the working muscles at the higher loads. These changes seem to be beneficial and to aid efficiency[2]. This adjustment, if properly understood, might throw light on the underlying mechanisms of thermal control in general. It might equally be induced by modifications of peripheral sensation as by alterations in the hypothalamic centers. However, the effects of carbon dioxide on skin sensations and of exercise on sweating seem to oppose any theory of a peripheral origin for the phenomenon. The mechanisms concerned in such adjustments remain completely unknown.

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EXOPHTHALMIC GOITER IN CHILDREN: TREATMENT WITH PROPYLTHIOURACIL

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The cause of exophthalmic goiter remains a mystery despite the great advances that have been made in its diagnosis and treatment. We are fortunate that treatment, even though essentially empirical, is usually successful.

Exophthalmic goiter in children presents all the problems of exophthalmic goiter in the adult, plus others due to immaturity, active growth, and changing metabolism. In this paper we wish to discuss our experiences with 26 cases of hyperthyroidism in children 16 years of age or younger. Eight of these have been treated with thiouracil or propylthiouracil. These we will consider in detail to show some of the responses to this type of therapy.

Diagnosis of hyperthyroidism in children is based on symptoms, signs, and basal metabolic determinations.

Symptoms are of two types: 1, those that are similar to those of adults and, 2, those that may be present or are more prominent in young people. The majority of children have signs and symptoms identical with those of adults, including symmetrical enlargement of the thyroid gland with thrill and bruit, exophthalmos, tremor, either actual weight loss in spite of ravenous appetite or weight remaining stationary when it should be increasing, nervousness, tachycardia, palpitation, warm and moist skin, general weakness, easy fatigability, quadriceps weakness, heat intolerance, elevated systolic and low or normal diastolic blood pressure, dyspnea, dorsal curvature of the distal phalanges, and irritability.

Certain other complaints may be prominent in children and may be quite misleading in the making of an accurate diagnosis. Important in this group are gastrointestinal symptoms (nausea, vomiting, and different types of abdominal pain), high susceptibility to upper respiratory infection, delayed or irregular menses, sleep disturbance (insomnia, restlessness, or talking in sleep), frequent epistaxis, marked personality changes with nervousness, temper tantrums, crying spells, headaches, and fainting. These children often give a history of an enlarged thyroid gland for from one to several years and may have been taking iodine for colloid goiter. The blood pressure findings are significant in children, 140 over 50 being a typical recording. The frequency of upper respiratory infections in some of these children increases the difficulty of getting a basal metabolic determination that is accurate.

Treatment must be suited to the individual case. There are 3 types of therapy: rest, operation and drugs, which may be used singly or together, depending on the individual need.

A program of rest with discontinuance of school, restricted activity, long hours of sleep with frequent daytime rest periods, a high caloric diet, and, if necessary, mild sedation is valuable. This frequently will alleviate the symp-

toms and carry a young patient along until he is a little older before undergoing operation. An occasional patient with mild toxic symptoms of short duration may be treated solely by this method. Adequate attention to psychosomatic aspects of the disease and to the education of the parents is essential in such a program.

As in adults, the surgical treatment of exophthalmic goiter in children gives excellent results in a high percentage of cases. Indications for operation are (1) the determination, based largely on experience, that operation is the best treatment for the particular patient; (2) failure of medical therapy, including a lack of response and development of complications such as leukopenia; and (3) persistence of an enlarged gland in spite of regression of toxicity after medical therapy.

Careful preöperative preparation is essential to successful surgery, including a rest program as outlined above, combined with the use of iodine and antithyroid drugs, such as propylthiouracil and methylthiouracil. Propylthiouracil causes a marked increase in the vascularity of the gland, making operation technically difficult. When antithyroid drugs are used, they should be discontinued 2 weeks prior to operation and iodine should be used to involute the gland. Iodine alone is excellent in the preöperative preparation of these patients, and for the past year we have used Lugol's solution only, without propylthiouracil, except in the most toxic cases. Operation should not be performed until the patient is gaining weight, the pulse rate has decreased, the basal metabolic rate is declining, and toxic symptoms are in remission.

Subtotal thyroidectomy is the operation of choice. In this clinic we have used superficial cervical nerve block anesthesia since 1928, in preference to the older method of infiltration. We use 1½% procaine with no adrenalin. Children 12 years of age and older given adequate preöperative sedation (pantopon, scopalamine, and nembutal, the dosage depending on weight and age) tolerate this well. The same surgical technique is used as in adults, this being an intracapsular excision of hyperplastic thyroid tissue, preferably with the electro-surgical knife. Considerable time and effort is spent prior to operation obtaining the confidence of the child, and the fact that no general anesthetic has ever been used testifies to the success of these efforts.

Postoperative care is extremely important. One advantage of nerve block anesthesia is that the patient is able to cooperate immediately and be given frequent oral doses of Lugol's solution. Ten to 15 doses of 10 drops of Lugol's solution are given on the day of operation, 4 doses in the first postoperative hour, 10 doses the second day, and 3 times a day thereafter until discharge. Rarely it may be necessary to give iodine subcutaneously, by proctoclysis or by duodenal tube. We do not use it intravenously. Iodine therapy after discharge from the hospital depends on the response of the patient. In some cases it may be discontinued after weeks, and in others it may have to be used for months or occasionally indefinitely.

The program of rest and high caloric intake is essential with the gradual increase in activity. We have found that the patient's weight is the best index of response to treatment and insist that a substantial gain be made the first 3 months after operation.

Medical treatment of hyperthyroidism is much in vogue, with thiouracil, thiourea, thiobarbital, propylthiouracil, and methylthiouracil receiving the most attention. Radioactive iodine is receiving much study, but results have been variable, some patients showing early favorable response only to relapse later.

In others the response has been encouraging but sufficient time has not yet elapsed to consider the patient cured.

We have used thiouracil and propylthiouracil on 8 of these patients. Response has been so varied that a brief individual discussion of each case is necessary. For the past 2 years propylthiouracil has entirely replaced thiouracil in our therapy. These will be discussed in the chronological order in which we saw the patients in order to show the changes in concepts.

CASE 1. (a) Exophthalmic goiter in 12 year old girl who has a basal metabolic rate of +33% and is 21 pounds underweight. (b) Same patient 2 months after antithyroid therapy. Her basal metabolic rate is +5% 1 year after stopping therapy.

Case Reports. CASE 1. H. B., a white female aged 12 years, was first seen on Sept. 9, 1944. She had an exophthalmos of 3 months' duration and swelling of the neck for 2 months, along with palpitation, extreme nervousness, and tachycardia, and was 21 pounds underweight. She had been taking iodostarine for 2 months. Her basal metabolic rate was +10%. It was thought clinically that she was probably iodine-fast. She was observed for a month, during which time her toxic symptoms increased. On October 10 her basal metabolic rate was +33%. She was placed on thiouracil, 0.1 gm. twice a day. She stayed on this dosage until June 8, 1945, when the drug was stopped. At this time she had gained 15 pounds, was free of toxic symptoms, and had a basal metabolic rate of +7%. She got along satisfactorily until Feb. 28, 1946, when symptoms recurred. She lost 7½ pounds, and her basal metabolic rate was +24%. She was put on thiouracil, 0.1 gm. twice a day. On April 11 her white cell count was 4,150 and thiouracil was stopped. On May 2 it was found that she had lost 2½ pounds and her blood pressure was 142 over 62, and her pulse was 132. On July 22 she was placed on propylthiouracil, 25 mg. 3 times a day. Five weeks later her white blood count was 4,060. In December, 1946, propylthiouracil was discontinued as she was well. She has remained well since.

CASE 2. R. N., a 12 year old white female, was first seen Sept. 4, 1944, having been ill 2 years. She was 23 pounds underweight and had a ravenous appetite, alternating diarrhea and constipation, tremors, nervousness, "heart pains", and temper tantrums. Her

blood pressure was 118 over 55 and her pulse 110. She was hospitalized and placed on thiouracil, 0.1 gm. 3 times a day. On November 1, she developed a skin rash on her thighs. Thiouracil was discontinued. She was placed on Lugol's solution and prepared for operation, and on December 18 a right lobectomy and isthmectomy were performed. On March 3 the left lobectomy was done. She made excellent recovery. On August 27 a nodule was felt in the right upper lobe. On June 26, 1947, her neck was enlarged and toxic symptoms recurred. She was placed on propylthiouracil, 50 mg. 3 times a day. On July 12 her white blood cell count was 4,200, but she was continued on the drug. Her disease was controlled with propylthiouracil until May, 1948. On June 2, 1948, operation was performed again for a large hyperplastic gland. Seven days later she was discharged with a basal metabolic rate of +10% and a pulse of 72.

CASE 2. (a) Severe case of exophthalmic goiter in 12 year old child. Following skin eruption from thiouracil, a thyroidectomy was performed. (b) Same child developed a recurrence 3 years later that failed to respond to propylthiouracil. After further surgery the disease is arrested, and the basal metabolic rate remains normal.

CASE 3. A. F., a 10 year old white female, was first seen Feb. 2, 1946. She had an enlarged thyroid gland, an exophthalmos of 2 months' duration, tremor, warm moist skin, and a ravenous appetite. Three weeks before her metabolic rate was reported as +62% at another institution. After three weeks of iodine it was +24%. Her blood pressure was 140 over 60, her pulse 120, and her weight 85 pounds. She was placed on propylthiouracil, 25 mg. three times a day. In September she went back to school half time. In April, 1947, she was without propylthiouracil for three weeks, lost 4½ pounds and became hyperactive. Propylthiouracil was resumed until June 29, 1947, when it was discontinued. At the present time, 16 months later, she is well and is attending school all day and weighs 114 pounds, has a pulse of 90, and a blood pressure of 125 over 60. Her metabolic rate was +10%. This is the most satisfactory result of propylthiouracil therapy we have seen in either an adult or a child and shows, despite statements in the literature to the contrary, it is at least possible to arrest the disease in some instances. One always hesitates to speak of a cure in exophthalmic goiter by any manner of treatment.

CASE 4. M. T., a white female aged 8 years, was first seen Sept. 14, 1946. Symptoms were extreme nervousness, insomnia and restless sleep, tremendous appetite, intolerance to heat, frequent sore throats, enlarged thyroid gland, tachycardia, and quadriceps weakness. Her blood pressure was 126 over 50 and her pulse was 158. She was placed on Lugol's solution for 2 weeks. She gained 3½ pounds, was less nervous, and felt better. On September 25 she was started on propylthiouracil, 25 mg. twice a day. Slow improvement oc-

curred until Jan. 18, 1947, when she contracted infectious hepatitis, as did her parents and several classmates. Propylthiouracil was stopped and she was placed on iodine for one month; then propylthiouracil was resumed and improvement continued. In February, 1948, she was free of symptoms, but her thyroid gland seemed larger than ever. In July, 1948, she appeared clinically well, and her basal metabolic rate was normal, so the drug was discontinued. In 4 weeks her basal metabolic rate had risen to +33%, and she was losing weight and becoming toxic, so the drug was again resumed. She again became normal. Further observation is warranted, but operation will probably eventually be necessary.

CASE 6. R. S., an 11 year old white female, was first seen Nov. 2, 1946. Her neck had been enlarged for 8 months, she was extremely nervous, exophthalmos was present, and there

CASE 3. (a) Exophthalmic goiter in 10-year old child who is on the verge of crisis and whose basal metabolic rate is +62%; weight 85 pounds; and pulse, 140. (b) Same child after stopping all therapy; basal metabolic rate, +10%. She received propylthiouracil for 1 year. She now appears clinically well, weighs 128 pounds, and has a pulse of 74.

CASE 5. N. R., a 13 year old white female, was first seen on Sept. 30, 1946, with symptoms of nervousness, heat intolerance, palpitation, weight loss, and increased appetite. Before our examination she had been on iodine for 2 months and thiouracil for 2 weeks with no improvement. She had a greatly enlarged thyroid gland with no thrill or bruit. Her pulse was 120 and her blood pressure was 142 over 40. There was stare but no exophthalmos. She was quite toxic. She was hospitalized and placed on propylthiouracil, 25 mg. 4 times a day. By April 21 all symptoms of hyperthyroidism were gone and she had gained 19 pounds. However, her thyroid gland continued to be greatly enlarged. On May 5, 1947, a subtotal thyroidectomy was performed on a large hyperplastic gland containing some adenomatous tissue. Since then she has remained well but has been on a reducing diet as she gained too much weight. She was continued on iodine for 6 months. Her last basal metabolic rate on Jan. 6, 1949, was +29%.

was a 13 pound weight loss in 6 months. She had been on Lugol's solution for 7 months. Her basal metabolic rate was +35%; her blood pressure, 134 over 44; and her pulse, 128. She was placed on propylthiouracil, 50 mg. twice a day. Twenty-two days later her white blood count was 2,500. The drug was discontinued, and she was placed on Lugol's solution. At this point contact was lost with the patient.

CASE 7. P. U., a 16 year old white female, was first seen Feb. 20, 1947. She had been

well until Jan. 23, 1947. At that time she was hospitalized for 2 weeks with symptoms of nausea, vomiting, diarrhea, and fever. She had had tachycardia and weakness of the legs since then. She had a moderate tremor, a pulse of 148, a blood pressure of 144 over 24, a weight loss of 14 pounds in 2 weeks, a warm moist skin, symmetrical enlargement of the thyroid with thrill and bruit, and quadriceps loss. A systolic murmur was present over the aortic and mitral areas. She had been on thiouracil for 10 days before admission. This was changed to propylthiouracil, 50 mg. 3 times a day. Three months later on April 22 she had gained 10 pounds; her blood pressure was 128 over 70, and her basal metabolic rate was +11%, and all toxic symptoms were gone. On July 23 propylthiouracil was discontinued. On August 26 her symptoms had returned.

She was definitely hyperthyroid with a basal metabolic rate of +43%. She was placed on iodine, and on September 10 a subtotal thyroidectomy was performed. She made a normal recovery, and when seen on May 27, 1948, she was well. She was continued on iodine until September 13. On Nov. 13, 1948, she resumed Lugol's solution, at which time her basal metabolic rate was +35% There was a weight gain of 22 pounds, and she appeared normal.

Case 8. M. G., a 16 year old white female, was first seen on Dec. 12, 1947. For 5 months she had been under her doctor's care for nervousness and loss of "pep". She had been told she had a goiter and had been given iodine. She had gained 11 pounds during this time but felt no better. She was jittery and constantly making purposeless movements. She was intolerant to heat and fainted frequently. She had a pulse of 116, a blood pressure of 142 over 60, exophthalmos, moderate tremor, and a symmetrically enlarged thyroid with thrill and bruit. In addition, for 6 months she had had definite voice change; it had become husky and gave her poor enunciation. Her basal metabolic rate was +49%. On December 2 she was started on propylthiouracil, 50 mg. 3 times a day. On January 3 she was worse; there was a 6 pound loss of weight, a basal metabolic rate of +70%, and increased nervousness. Propylthiouracil had been stopped 2 weeks before because of a white blood cell count of 4,500. It was thought that she was on the verge of a thyroid crisis. She was hospitalized and placed on Lugol's solution. On Jan. 16, 1948, a subtotal thyroidectomy was performed on a large hyperplastic intrathoracic goiter. One month later her basal metabolic rate was 0%; pulse, 70; and blood pressure, 120 over 84. There was a weight gain of 18 pounds. Since then she has been well, except that a reducing diet has been necessary.

In all of these cases the patient was placed on a regimen of rest, high caloric diet, and discontinuance of school, in addition to medication.

Summary and Conclusions. Twenty-six cases of exophthalmic goiter have been observed in children ranging in age from 8 to 16 years. Symptoms and treatment have been discussed, especially the results of thiouracil and propylthiouracil in 8 cases so treated. The following conclusions seem warranted:

1. Depression of white blood cells must be carefully watched for in the use of thiouracil and propylthiouracil. Four of 8 patients treated with these drugs developed white counts below 5,000, although there were no serious complications. Propylthiouracil is much safer than thiouracil, which should no longer be used.

2. These drugs have a goitrogenic action as evidenced by Cases 4 and 5, in which, although toxicity was relieved, the continuing large size of the gland made it necessary to perform thyroidectomy.

3. Early diagnosis in some cases may be difficult, for two reasons: 1, atypical symptomatology; and, 2, the masking of the clinical picture by previous treatment.

4. Individual response to these antithyroid drugs is uncertain in children, and there is no rule to determine in which cases they will be successful.

5. At present, the best place for these drugs is probably in preoperative preparation, or in patients in whom it may be necessary to delay operation.

6. The fact that in only one patient with hyperthyroidism was the disease apparently permanently arrested by propylthiouracil indicates that operation is still the method of choice in the treatment of these patients.

7. Iodine should be given to all patients prior to and following opera-

tion. Its use is especially indicated following propylthiouracil to decrease the vascularity of the gland and reduce bleeding at operation.

8. Cervical nerve block anesthesia was successfully used in all patients requiring thyroidectomy, no general anesthesia being necessary.

9. These patients must have an even more careful postoperative regimen than that required for adults. The importance of a high caloric diet, restricted activity, rest, and iodine is stressed.

LIVER AND KIDNEY FUNCTION IN ROCKY MOUNTAIN SPOTTED FEVER*†

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Rocky Mountain spotted fever is a severe generalized infection which is known to cause damage to many organs. Cases are now recognized with some frequency over wide areas of the United States. More instances of the disease are reported currently from the eastern seaboard and southeastern states than from the west. The *anatomic changes* produced can be demonstrated by pathologic techniques at autopsy. Disturbances of function have been observed clinically in the course of the disease, but few attempts have been made to evaluate the *physiologic alterations* in specific organs. We have previously described alterations in the serum proteins and in electrolytes of the blood, as well as the circulatory changes occurring in the disease[10,13]. These observations suggested that some functions of the liver and kidney might be disturbed.

In the treatment of infectious diseases, chemotherapy or specific immunotherapy is directed toward eradication of the etiologic agent. Such therapy is not aimed primarily at the prevention or control of physiologic disturbances which are induced in the host by the infectious process. In the hope of obtaining information which would permit supportive therapy to prevent or correct such disturbances, studies of several functions of the liver and kidney were done to determine: 1, the degree of the physiologic disturbances; 2, their relation to the clinical severity of the disease; 3, the time in the course of the disease at which changes are maximal; and, 4, the degree to which function is restored with recovery.

Plan. During the years 1942 to 1947 inclusive, 26 cases of Rocky Mountain spotted fever have been studied intensively in the North Carolina Baptist Hospital; 19 additional cases were seen for too short a period of time to be included in this report. Of the patients studied intensively, 16 were under the age of 15 years and were cared for on the pediatric service; the remaining 10 were treated on the medical service. Eight patients—5 children and 3 adults—were studied before the addition of high protein diets with vitamin supplements to our program of supportive therapy; 18 patients—11 children and 7 adults—were studied after this form of therapy was made routine[11]. Seven cases were classified as mild, 10 as moderately severe, and

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† Doctors William L. Venning and Weston M. Kelsey assisted in the care of the pediatric patients.

6 as severe; 3—all in children—were fatal. The criteria for classification of the cases have been previously published[12].

The attempt was made to perform studies on each patient at 4 periods in the course of the disease: (1) as soon as possible after admission to the hospital, (2) at the clinical peak of the disease, (3) during convalescence in the hospital, and (4) during recovery after discharge. Since so many of the patients were small children and so many were critically ill—often comatose, edematous, and incontinent—it was difficult to do all of the studies planned on each patient. Furthermore, many patients were admitted when the disease was well advanced and were near the clinical peak when they were first seen. Only a few returned after recovery. Data on two or more periods are available in about one-third of the cases; 8 patients had serial liver function studies made at two periods, and 8 had kidney function tests at two periods.

Methods. TESTS OF LIVER FUNCTION. Studies were designed to measure carbohydrate conversion and storage by the oral galactose tolerance test; "detoxification" by the conjugation of orally or intravenously administered sodium benzoate to hippuric acid; the formation of proteins by the prothrombin time and the albumin and globulin levels; pigment metabolism by the quantitative serum van den Bergh test and the removal of intravenously injected bromsulfalein.

The *galactose tolerance* was judged to be abnormal if more than 3 gm. of reducing substance was excreted by the kidney in 5 hours following the ingestion of 40 gm. of galactose on a fasting stomach.

The excretion in 4 hours of at least 2.7 gm. of *hippuric acid*, calculated as sodium benzoate, after the oral administration of 5.9 gm. of sodium benzoate, was taken as normal. The excretion of 0.7 gm. in 1 hour after the intravenous injection of 1.77 gm. of sodium benzoate was likewise regarded as normal.

In children the adult doses were used for both the galactose tolerance and the hippuric acid tests; the normal range of values is less firmly established in this age group, but for the purpose of this experiment the normal values were considered the same as in adults.

The *prothrombin time* was determined by the Quick method in adults and by a micromethod in children[21]. If the prothrombin time was prolonged, vitamin K was administered orally or parenterally and its effectiveness evaluated by serial determinations; 1 mg. of menadione per day was included in the high-protein supplementary feeding which was administered routinely to all patients after July, 1944. A prothrombin activity (control in seconds/prothrombin time) of less than 85% was regarded as abnormal[22].

Serum levels of *albumin and globulin* were determined by the micro-Kjeldahl technique. Values below 3.5 gm. % for albumin or 1.5 gm. % for globulin were taken as abnormal.

For the *bromsulfalein (BSP) test* 5 mg. per kg. of body weight was injected intravenously; as many blood samples as possible were drawn after 5, 10, 15, 30, 45 and 60 minutes. Because of the difficulty in finding veins, especially in the children, only 2 or 3 samples were usually obtained. Retention of more than 10% of the dye at 15 minutes, 5% at 30 minutes, or any at all after 45 minutes was taken as evidence of abnormal function.

Serum bilirubin was measured by the standard van den Bergh technique; values above 0.8 mg. per 100 cc. were regarded as abnormal.

TESTS OF KIDNEY FUNCTION. The excretory power of the glomeruli was measured by urea clearance tests and nonprotein nitrogen (NPN) determinations; the excretory power of the tubules by phenolsulphonphthalein (PSP) tests; and damage permitting the escape of elements from the blood by the presence of albumin in the urine and by microscopic examination.

The *urea clearance* was determined by comparing the urea nitrogen in the blood with that in a sample of urine collected over a period of at least 6 and usually 12 hours; standard analytical techniques were employed. A value of 50% or less of normal was interpreted as indicating abnormal function; a value above 70% was accepted as indication of adequate function. Values between 50 and 70% of normal were interpreted as demonstrating questionable renal damage.

Phenolsulphonphthalein (PSP) excretion was determined in specimens of urine voided 15, 30, 60, 90, and 120 minutes after the intravenous injection of 1 cc. of dye. Excretion of 65% or more of the dye in two hours was regarded as normal in adults. The same dose was used in children, but an excretion

of 50% was judged to be normal.

Blood levels of *nonprotein nitrogen* were determined by standard methods. Values above 40 mg. per 100 cc. were regarded as abnormal.

Tests for *urinary albumin* were performed by boiling a sample of urine after the addition of acetic acid.

Microscopic examination of the urine was done on 15 cc. samples of voided urine; the samples were centrifuged in adults, but not in children.

Results. The results are summarized in the table. In order to save space, detailed data are not included; in the analysis of data in some instances where different tests were done on successive days, they have been considered as if they were done on the same day.* Despite the unavoidable lack of baseline tests made before the illness began, a measure of control was afforded by the return to normal values after recovery and by comparison with figures for similar tests performed in other infectious diseases.

TABLE 1. THE NUMBER AND SEVERITY OF CASES STUDIED COMPARED WITH THE NUMBER SHOWING ABNORMALITIES OF FUNCTION BY THE TEST INDICATED

	Number of Cases Studied			Number with Liver Damage			Number with Kidney Damage
	Adults	Children	Total	Hippuric	BSP	Albumin	Urea Clearance
Fatal		3	3	1	1	2	1
Severe	2	4	6	1	1	3	2
Moderate	4	6	10	5	2	9	4
Mild	4	3	7	3	2	4	2
TOTAL	10	16	26	10	6	18	9
Before high protein diet	3	5	8	6		7	5
After high protein diet	7	11	18	4	6	11	4
TOTAL	10	16	26	10	6	18	9
Before clinical peak				0	2	8	4
At clinical peak				6	1	8	2
After clinical peak				4	3	2	3
TOTAL				10	6	18	9

TESTS OF LIVER FUNCTION. *Galactose tolerance tests* were done on 9 patients and were repeated in 4 patients. All gave a negative reaction. In 5 instances simultaneous hippuric acid tests showed a decrease in function.

Hippuric acid excretion was satisfactorily determined in 16 cases. In 5 cases multiple tests were done. In 13 patients the hippuric acid excretion was less than normal at some time, usually at or just after the clinical peak of the disease, about the third week of rash. In 6 instances less than 1 gm. was excreted on the oral test. Nine tests gave normal values. In no instance was the hippuric acid excretion abnormal after the twenty-first day of rash. In 2 patients with abnormal tests the hippuric acid excretion reverted to normal before discharge. In general the defect in conjugation paralleled the clinical severity of the disease, though 3 patients with mild cases did have abnormal tests. In 3 instances simultaneous NPN determinations were above 40 mg. per 100 cc., while in 5 instances the NPN was normal. Simultaneous PSP tests gave normal values in 3 cases.

The *prothrombin time* was determined in 11 patients. In 5 cases the

* Detailed data are available and figures on specific tests in an individual can be furnished on request.

prothrombin time, at some time during the course of the illness, was increased five seconds or more as compared with the control; the prolongation usually occurred at about the clinical peak of the disease. Only 2 patients had markedly abnormal tests, however. The percentage of activity in these 2 patients was 10 and 13%; in the remaining 3 cases the activity was 55 to 78%.

One child, who had a normal prothrombin time on admission, received prophylactic oral doses of menadione (1 mg. daily) for 5 days. At the end of that time (tenth day of rash) the prothrombin time was two minutes against a control of 14 seconds (18% activity), and the following day it was 3 minutes against a control of 18 seconds (10% activity). Within 12 hours after 1 mg. of vitamin K was given parenterally, the prothrombin time returned to normal and remained so. One boy had a slightly elevated prothrombin time on admission. One day later the prothrombin time was 2 minutes and 30 seconds, in comparison with a control of 20 seconds (13% activity). The prothrombin time remained at this level for 7 days (from the third to the tenth day of rash) in spite of the daily parenteral administration of 4 mg. of vitamin K. Both of these cases were classed as severe.

In all instances the prothrombin time was normal by the time of discharge from the hospital.

Serum levels of *albumin and globulin* were determined in all but 2 patients. In these 2 the total serum proteins were below 5 gm. %; they rose to 6.5 gm. by discharge. Albumin values below normal were found at some time in 18 out of 24 patients; in 7 they returned to normal by discharge. Reduced globulin levels were found in 4 patients; in 2 the value returned to normal by discharge. In 2 patients globulin levels above 3.5 gm. per 100 cc. were observed; in both they were still rising at discharge.

Seven out of 7 patients observed before the institution of a high protein diet as part of the therapeutic regimen had lowered albumin levels. In only 2 had the level risen to normal by discharge. In contrast, 11 out of 17 patients treated with high protein diets had reduced albumin values, and in 5 of these the value had returned to normal by discharge.

The serum protein levels were lowest at or just before the clinical peak of the disease. The drop in proteins was influenced by the clinical severity of the disease, the duration of the illness before admission, and the amount of protein taken in the diet.

Serum bilirubin values were obtained on 13 patients. In only one patient was the value elevated, and then only to 1.4 mg. per 100 cc., though it remained elevated from the tenth through the thirty-first day of rash. Liver damage was demonstrated in this patient by hippuric acid tests performed on the eleventh and sixteenth days of rash.

Eighteen *bromsulfalein (BSP) tests* were carried out on 14 patients. In 6 instances slight retention of the dye was demonstrated; in 2 cases in which several different tests were done, retention of BSP was the only indication of liver damage. In 3 patients the bromsulfalein test was normal, while the hippuric acid test showed a low excretion. In one other the hippuric acid and BSP tests were in agreement. Usually retention of the dye was noted at about the clinical peak of the disease, or early in convalescence, though in 2 cases dye retention was observed before the clinical peak.

Tests of Kidney Function. *Urea clearance* tests were satisfactorily completed on 13 patients. One child showed definite evidence of renal damage, with an excretion of less than

50% of normal; she subsequently died from the disease. In 8 patients the clearance was between 50 and 70% of normal; 3 of these patients were over 40 years of age. Four patients showed unimpaired urea clearance with an excretion of 70% of normal or greater. In 2 instances abnormal urea clearance tests reverted to normal by the time of discharge. The degree of damage could not be correlated with the clinical severity of the disease. The reduction in function usually occurred at or before the clinical peak of the disease, though 3 abnormal tests were observed after the peak.

Phenolsulphonphthalein (PSP) excretion tests were satisfactorily completed in 9 patients. All excreted normal amounts of the dye in 2 hours. In all instances a greater amount of dye was excreted in the first specimen than in any other—a fact which further supports the conclusion that the tubular excretory function was not impaired. In 3 patients on whom a urea clearance test was also run, the results indicated a questionable impairment of function.

Nonprotein nitrogen levels were determined in all but 7 patients, and were followed serially in 13 patients. In 2 cases the NPN exceeded 70 mg. per 100 cc. before the clinical peak of the disease. In 5 cases the NPN was found to be between 40 and 70 mg. per 100 cc. at some time. In 12 patients the level did not exceed 40 mg. per 100 cc. at any time. In 4 patients an elevated NPN returned to normal by the time of discharge, but in one it was still 44 mg. per 100 cc. In 2 others repeat determinations were not done. Since the fluid and protein intake, blood pressure, urinary output, and renal function all affect the level, it was impossible to correlate the changes with the severity of the illness.

Albuminuria of varying degrees was observed at some time during the course of the illness in 10 patients. Only 2 patients had a frank albuminuria, with a 2 plus reaction; 5 patients showed 1 plus reactions, and 3 patients had a trace of albumin. In most instances albuminuria was found early in the course or at the clinical peak of the disease; it usually persisted for two or three days only, and then disappeared. In 5 patients who had had albuminuria, the reaction was negative by the time of discharge. Since the amount of albumin in the urine is influenced by fever and by the urine volume, it was not possible to correlate the degree of albuminuria with the clinical severity of the disease.

Microscopic examination revealed occasional granular or hyaline casts in only 8 cases. One patient had frank hematuria, with numerous red cells in the centrifuged urinary sediment, but the abnormality persisted only one day; a simultaneous determination of the prothrombin time was not done. Four patients had slight hematuria (2 to 5 red blood cells per high power field) for periods of 1 to 3 days. In most instances microscopic abnormalities in the urinary sediment were found at about the clinical peak of the disease; rarely were changes observed during convalescence. No alterations suggestive of acute glomerulonephritis were found at any time.

Discussion. LIVER FUNCTION. Disturbances in liver function were observed in patients with Rocky Mountain spotted fever. Alterations were greatest in the conjugation of benzoic to hippuric acid and in the serum levels of albumin and globulin, but changes were also observed in the bromsulfalein retention test, the van den Bergh reaction, and the prothrombin time. The degree of the functional disturbance usually was not marked, but was roughly parallel to the clinical severity of the disease.

Definite alterations were seen even in mild cases. The maximal changes in the prothrombin time and serum protein content occurred at about the clinical peak of the disease. Alteration in hippuric acid excretion was most frequent at the clinical peak, but also occurred during convalescence; no abnormal test was observed early in the course of the disease. Bromsulfalein retention was seen at each period tested. All functions tended to return toward normal as the patient recovered.

Alterations in prothrombin time reflect one function of the liver—synthesis of complex molecules. The prothrombin time is a measure of the prothrombin contained in the circulating blood at the moment; it does not indicate stores. The 2 cases in which marked changes in the prothrombin time occurred were both severe, and in both cases the change appeared overnight. The prompt response of parenteral vitamin K in one case would indicate that liver function was not greatly impaired. The total serum proteins at the time were only 3.9 gm. %. A BSP test performed 6 days previously was normal. The other patient did not respond promptly to parenteral administration of vitamin K, and was so ill that he was not expected to recover[12]. The galactose tolerance and BSP tests were normal at the time; a satisfactory hippuric acid test was not obtained until one week after the prothrombin time reverted to normal at which time 4 gm. was excreted.

Unfortunately, no determinations of the prothrombin time were obtained in 2 of the 3 fatal cases; in the other the time was normal 5 days before death. None of the patients had received salicylates or sulfonamides (which are known to induce liver damage and to prolong the prothrombin time) for several days before the abnormalities were noted.

A comparison of the prothrombin time and serum albumin level is not possible, because many of the patients received preformed protein intravenously, in the form of whole blood, plasma or purified human albumin, as part of the supportive therapy[11,20]. These measures, as well as the high protein diet, probably would have less direct effect upon the prothrombin time than upon the albumin level.

Hippuric acid excretion was altered in each of 6 patients tested before a high protein diet became part of our therapeutic regimen. After routine treatment with forced feedings of a high protein diet was instituted, the abnormality was observed in only 3 of 18 patients. The fact that the albumin content was decreased in each of 7 patients tested before introduction of the diet, and in only 11 of 17 patients after use of the diet was begun, lends further support to our belief that a high protein diet helps to prevent liver damage. In addition, the diet reduces the amount of preformed protein required for support of the circulation and seems to minimize the development of peripheral circulatory collapse and edema[13].

Pathogenesis of liver damage in infectious diseases. The pathogenesis of the liver damage occurring in Rocky Mountain spotted fever is not clear. Though the rickettsias are characteristically found intranuclearly in the endothelium and smooth muscle cells of arterioles, vascular lesions in the liver are not prominent. In fatal cases small areas of necrosis have been observed in the midzonal areas away from arterioles[31]. In the absence of myocardial failure, the liver was palpable in only one of our patients. In none of the 3 fatal cases was the liver found to be enlarged at autopsy; microscopic examination showed slight degeneration of parenchymal cells with

minimal vacuolization in only 1 patient. This child had marked purpura and was treated before the introduction of the high protein diet. We have not attempted serial aspiration biopsies of the liver to correlate functional and anatomic damage in this disease.

In certain other infections, such as epidemic virus hepatitis, yellow fever, and homologous serum jaundice, hepatic cells apparently are directly parasitized. Hepatitis has been observed following interstitial infections of the liver with bacteria such as the beta hemolytic Streptococcus and Escherichia coli. In other diseases the reticuloendothelial (Kupffer) cells in the liver become filled with larger intracellular parasites such as the Leishmania. In infestations with still larger parasites, such as the Schistosoma, the eggs or adult parasites are filtered out in the venous channels of the liver and induce a local foreign body reaction with marked scarring.

Functional liver damage has been observed in many infectious diseases; in few instances, however, have multiple tests been performed to measure different functions, or have tests been run serially. Except when there is direct parasitization of the liver cells or massive extracellular invasion by bacteria, spirochetes or larger parasites, function is seldom altered greatly. Reduction in function may occur during the acute febrile period or during convalescence. It has been noted that alterations develop most frequently about 3 weeks after the onset of any disease. In scarlet fever the changes occur at about the time complications develop, during the third week of illness[2,4]. In malaria the alterations in the cephalin-cholesterol flocculation, albumin-globulin ratio, and bromsulfalein excretion occur during the acute febrile phases of the illness[7,9,24,26]. Indeed, decrease in liver function has been observed in fever produced artificially without actual infection[1,18]. Studies have also been conducted in patients with chronic infectious arthritis, infectious mononucleosis, experimental infectious hepatitis, pneumococcal pneumonia, lymphogranuloma, and tuberculosis[6,14,16,19,23,29].

The exact mechanism by which changes in hepatic function occur without destruction or compression of liver parenchyma is obscure. Fever itself apparently will reduce the function of hepatic cells, but the changes quickly disappear as the temperature subsides. This mechanism may explain transient alterations appearing early in the course of a disease. It is possible that soluble products of the rickettsias of Rocky Mountain spotted fever might diffuse out of vascular cells elsewhere in the body and reach the liver through the blood, producing a direct hepatotoxic effect; however, the functional changes, except for those in pigment metabolism, usually occur too late to be due to such a mechanism. The alterations in function which have been observed in various chronic infections or late in the course of other acute infections (during the third week of illness, when convalescence is established) would suggest another mechanism. The immune balance has already been tilted by this time, and it seems late for an antigen-antibody reaction to be at fault, as it may be in the pathogenesis of circulatory failure[13]. Furthermore, hypersensitivity has not been demonstrated in patients with Rocky Mountain spotted fever. On the other hand, allergic liver necrosis has been demonstrated in hypersensitive animals after the injection of egg white[15]. In fatal cases of Rocky Mountain spotted fever microscopic lesions found in various organs resemble those seen in serum sickness—an illness which seems to be due solely to the

interaction of antigens and antibodies[17].

Prophylaxis against liver damage. A prolonged and severe illness reduces the intake of protective foods and exhausts the stores of many body substances. This situation may induce a metabolic imbalance which could duplicate that resulting from the experimental restriction of proteins and lipotropic substances to produce fatty livers[3]. In our experience a high protein diet with vitamin supplements has afforded some protection against liver damage in Rocky Mountain spotted fever. In therapeutic malaria, however, a moderate increase in the protein intake has afforded no protection against alterations in hippuric acid excretion[7]. In experimentally produced burns, where liver damage is known to occur, a high protein diet supplemented with methionine has tended to reduce the extent of protein catabolism as measured by nitrogen loss in the urine[5]. Presumably the liver would also be protected to some extent.

Measurement of liver damage. In any event, the defect in liver function occurring in Rocky Mountain spotted fever is not great enough to cause death, and is reparable with recovery. The introduction of effective specific antibiotic therapy with aureomycin and chloromycetin may reduce still further the incidence of abnormal liver function tests in this disease. From our experience we believe that a few selected tests—albumin and globulin levels, prothrombin time, and hippuric acid excretion—done in the second week of rash will detect functional liver damage and provide a good index of its degree. On the basis of the limited data available and the hemorrhagic character of the anatomic lesions, the response of the prothrombin time to parenteral injections of vitamin K may be helpful in estimating prognosis.

Kidney Function. Renal function is altered less than liver function in Rocky Mountain spotted fever, but the disturbance does not appear to parallel the clinical severity of the disease. A decrease in kidney function has been observed less frequently than alterations in the liver. Maximum changes appear earlier than with liver damage and seem to revert promptly to normal with recovery. The reduction in kidney function seen in patients past the age of 40 should not be attributed solely to the infection, since the amount of functioning renal tissue is known to be reduced by the ordinary wear and tear of advancing years. The reliability of the urea clearance test as a measure of renal function in children is not universally accepted, but no other tests gave conclusive evidence of renal damage. No changes have been observed which resemble those seen in glomerulonephritis.

In view of the high excretion of urinary nitrogen which occurs in Rocky Mountain spotted fever, as well as in other infectious diseases, and the minimal alterations in urea clearance tests, it is probable that the azotemia which has been observed in many cases is due, not to renal insufficiency, but to massive destruction of proteins or to reduced glomerular filtration caused by circulatory disturbances[8,10,11]. Circulatory disturbances affect renal function more than liver function. The distribution of body fluids, as determined by simultaneous measurements of the blood volume and extravascular thiocyanate fluid space, has been shown to be altered in Rocky Mountain spotted fever[13].

Pathogenesis of renal damage. The mechanism responsible for renal changes is obscure. Fever alone has been known to reduce the creatinine clearance in dogs[27]. In Rocky Mountain spotted fever vascular damage is produced by direct parasitization of

cells. In serum sickness and the experimentally produced vascular disease resembling periarteritis nodosa, renal lesions are pronounced and are accompanied by albuminuria; albuminuria has not been marked in our cases of Rocky Mountain spotted fever[25,28,30]. The time of occurrence of the renal damage does not fit with an antigen-antibody reaction. Such reactions, resulting in serum sickness, have been shown to decrease the excretion of chloride and water; a reduction in blood chlorides and retention of water have been observed frequently in Rocky Mountain spotted fever, but have not yet been shown to be due to a renal defect[10,12,28].

No specific measures have been devised which will afford protection against the temporary renal damage.

Summary. 1. Functional liver damage, roughly related in degree to the clinical severity of the illness, has been demonstrated by us in patients with Rocky Mountain spotted fever. Changes were most marked and most frequent in the hippuric acid excretion test, which usually showed the greatest alteration at or following the clinical peak of the disease. Reduction in pigment metabolism (as measured by the bromsulfalein retention test and the van den Bergh reaction) and reduction of the formation of complex molecules by the liver (as shown by the prothrombin time and the albumin and globulin contents of serum) were found during the acute febrile phase of the disease. All liver functions returned to normal during convalescence.

2. Functional renal damage was demonstrated occasionally in the course of Rocky Mountain spotted fever. Reduced urea clearance values and transitory albuminuria or hematuria were observed. The azotemia commonly found is probably caused by factors other than reduced renal function. The defect in renal function was slight in degree, occurred before, during or after the clinical peak of the disease, and returned to normal during convalescence; the degree could not be correlated with the clinical severity of the illness.

3. These changes are not specific for Rocky Mountain spotted fever and are not significantly different from those obtained in many other generalized infections.

4. The administration of a high protein diet—by forced feedings of a liquid supplement, if necessary—protects the liver against marked functional damage; it does not alter the function of the kidneys, though it may temporarily overload them.

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EMBOLIZATION WITH MATERIAL FROM ATHEROMATA

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Embolization of systemic arteries with material from eroded aortic atheromata has been recognized only recently as a clear cut histological entity, although it is by no means rare and references to its occurrence can be found in some of the older text books. Flory[5] devoted an excellently illustrated article to this problem, while Meyer[8] from Rössle's Institute, not being aware of Flory's paper, stated in a paper published only 2 years ago that he had discovered a new type of embolization.

The reasons for the delayed discovery of such a basic process are several, the foremost being misinterpretation of the findings as organizing thrombi, as pointed out by Meyer. Yet it remains amazing that lesions of this type are not generally familiar to pathologists.

The following report is a case in point:

Case Abstracts. Case 1. This 62 year old man was admitted because of "ashen color," labored respirations, restlessness and confusion. He had ecchymoses over buttocks and thighs and was bleeding from the rectum. The past history was noncontributory except for an episode of unconsciousness 4 months before this admission which had required hospitalization elsewhere. On admission here he was found to have a hard, large, nodular prostate. He had severe anemia, occult blood in the stool and only 5,000 platelets per c.mm. in the peripheral blood. The differential count suggested diffuse bone marrow replacement. The sternal marrow aspiration revealed tumor cells. Blood urea nitrogen was 107 mg. and creatinine 4.7 mg. per 100 cc. The urine contained 3+ albumin with a specific gravity of 1.021, 4 to 5 red blood cells per high power field and some granular casts. Despite supportive measures the patient died on the third day in the hospital. The clinical diagnosis was carcinoma of the prostate with widespread metastases.

This was confirmed at *autopsy* (14130). There was involvement of lymph nodes, lungs, right ureter and vertebral bone marrow with marked osteoplastic reaction. There was severe systemic arteriosclerosis with sclerosis of all the coronary artery branches with minimal narrowing. The myocardium showed focal necrosis which was ascribed to the anemia. Bilateral hydrothorax, pulmonary edema and acute hepatic congestion were present. There was severe atheromatosis of the aortic arch, the thoracic and abdominal aorta, as well as the splenic and left renal arteries. Many of these atheromata were eroded. The iliac veins were not thrombosed. Multiple acute splenic infarcts and healed renal infarcts were found. In the absence of valvular disease, mural thrombi of the heart and patent foramen ovale, it was postulated that the infarcts of spleen and kidneys were due to embolization of atheromatous material from the eroded aorta.

Microscopic examination of frozen sections from the infarcted areas of kidney and spleen revealed the vessels supplying these areas to be plugged by amorphous material embedded in which were found acicular spaces. When the Schultz test[14] was applied to these slides the colorless, doubly-refractile material in these slit-like spaces underwent the color changes typical of cholesterol (green in a few minutes and brown in 30 minutes). In addition to spleen and kidney, embolization could be demonstrated microscopically in the arteries of the following organs: pancreas, prostate, thyroid, jejunum, rectum, vertebral marrow, periosteum of the sternum and common

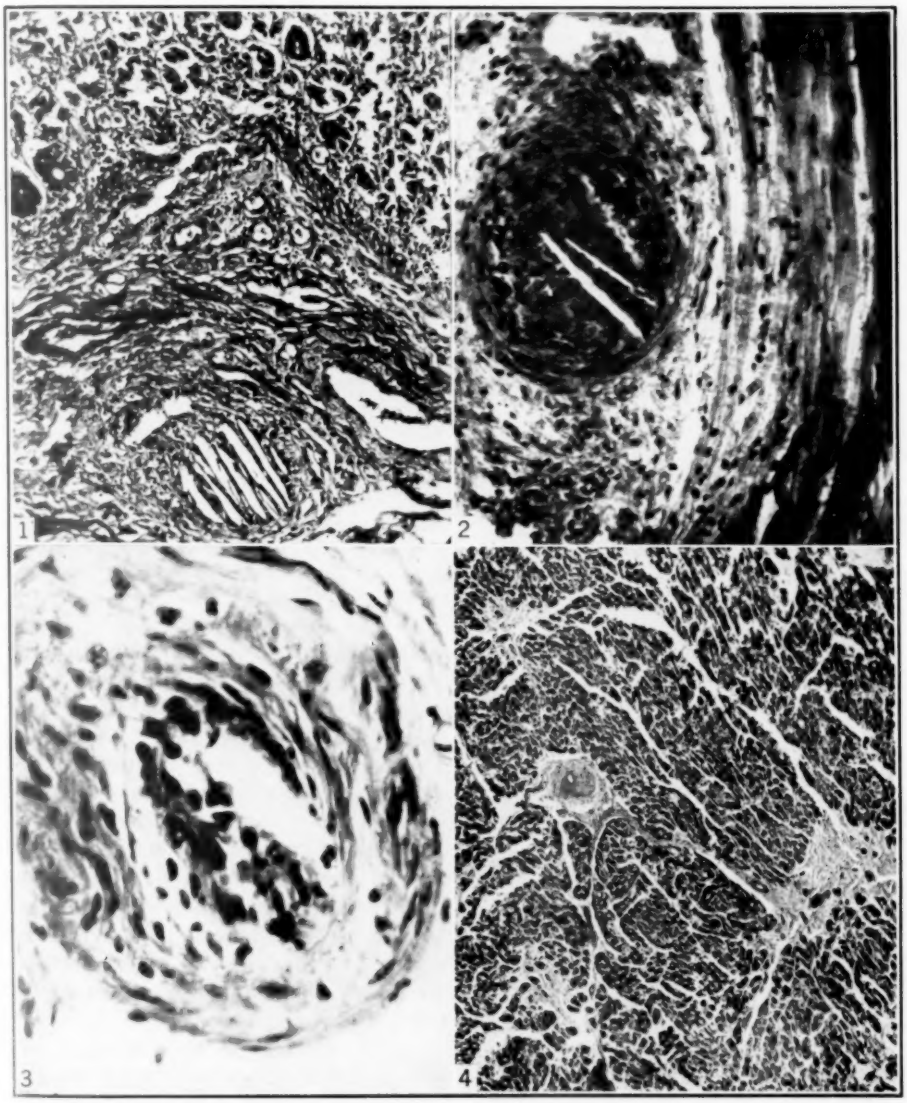

FIG. 1. CASE 1. Large submucosal artery in jejunum, containing acicular spaces in parallel arrangement with giant cell reaction (x 150).

FIG. 2. CASE 2. Acicular spaces and amorphous material in the lumen of intramural coronary artery branch with leukocytic (predominantly eosinophilic) reaction (x 350).

FIG. 3. CASE 2. Intramural coronary artery branch showing fibrous wall with inflammatory cells. Lumen contains similar cells surrounding large eccentrically located fusiform space (x 600).

FIG. 4. CASE 2. Intimal thickening of intramural coronary artery branch with 3 small scars in the surrounding myocardium. Same artery as in Fig. 3, at different level (x 50).

bile duct. Frequently there was typical foreign body giant cell reaction surrounding the intravascular cholesterol crystals.

This case then represents the most common form of atheromatous embolization, namely the chronic or even healed phase of embolization with atheroma material. Some of the involved organs, seen in this case, have either not been mentioned before or pictured as being involved by this type of embolization and it is for this reason that we show an illustration of the jejunum (Fig. 1).

The acute phase of this process appears to have escaped the attention of histopathologists and for this reason the following case is reported:

CASE 2. A 35 year old man of Armenian extraction was admitted because of "not feeling well" for several hours. While in the reception room he developed deep cyanosis with stertorous breathing and lapsed into coma. The heart beat and pulse became unobtainable and he died shortly thereafter.

Autopsy revealed the following pertinent findings (13563): Severe coronary arteriosclerosis with occlusion of the right coronary artery about 1 cm. from the ostium by a hemorrhagic plug. The heart weighed 375 gm. and was pale reddish-brown and flabby. All cardiac chambers were moderately dilated. Endocardium and valves were normal. There was a lentil-sized greyish patch in the posterior wall of the left ventricle. There was arteriosclerosis of the aorta, particularly of the descending thoracic and abdominal parts. There was no erosion of plaques in the aorta anywhere. *Microscopic study* confirmed the above findings and showed the occlusion of the right coronary artery as being due to hemorrhage into an atheromatous plaque. Acute and subacute myomalacia was found in the posterior wall of the left ventricle.

There was, however, one feature which at first could not be explained properly, namely the occurrence of inflammatory cells, among them many eosinophils, surrounding intramural arteries and extending into the broader septa of the vicinity. This was seen only in the posterior wall of the left ventricle and not in sections from other parts of the heart. A fortuitous frozen section accidentally supplied us with the correct answer (Fig. 2). This section showed arteries within the myocardium, surrounded by a dense inflammatory infiltrate and plugged by amorphous material containing acicular spaces, usually associated with cholesterol crystals. It was then decided to cut serial sections of the tissue block from the posterior wall of the left ventricle. Our expectations were substantiated as several arteries which at first showed only the inexplicable perivascular inflammation, in the serial sections revealed incontestable proof of occlusion by amorphous material containing slit-like spaces. This can only be interpreted as embolization with atheroma material from the right coronary artery inasmuch as there was no eroded atheroma anywhere in the aorta.

Careful scrutiny of the serial sections allowed chronological grading of the vascular lesions. Vessels surrounded by inflammatory cells with prevalence of polynuclears (and eosinophils) were felt to represent the most acute phase. Lesions where multinucleated giant cells are prominent represent a later stage. The oldest lesion found is characterized by fibrous thickening of the intima (Fig. 3). Lesions of this type were associated with small myocardial scars at a short distance from the occluded vessel. These scars could be traced to arterioles arising from the obstructed artery (Fig. 4).

This case brings up several new points. Firstly, embolization with atheroma material may arise from an artery other than the aorta—in this instance the right coronary artery. Secondly, myocardial scars may be due to this process, a fact which might be brought out by use of serial sections. Thirdly, the acute phase of this condition may impress as an arteritis with conspicuous eosinophilic polymorphonuclears. Whether this is due to an allergic response to the body's own proteins which are present in the atheroma we are not prepared to say.

CASE 3. The last case to be discussed concerns a 77 year old woman who was admitted for gangrene of the middle toe of the left foot. She had had pain in both legs for 2 months before admission, and a black spot in the area described was noted 10 days before admission. This spread with increasing pain. She had had a "heart attack" some 5 years before admission, which confined her to bed for several weeks. An electrocardiogram was not taken at the time. On admission she appeared acutely ill with a blood pressure of 120/80 and irregular pulse averaging about 72 beats per minute. She had kyphoscoliosis to the right and dullness at the right base with

diminished breath sounds in the same area. Her heart was enlarged to the left with a systolic murmur and apical gallop rhythm. Radial pulses were poor and so was the left femoral pulse. The patient died on the third hospital day while on penicillin therapy.

Autopsy (14159) revealed severe systemic arteriosclerosis. There was an arteriosclerotic occlusion of the superior mesenteric artery near its origin and an old occlusion of the anterior descending branch of the left coronary artery with a healed infarction of the anterior wall of the left ventricle. The heart weighed 550 gm. The right and left ventricles were dilated and hypertrophied. The mitral ostium admitted 2 fingers and therefore did not participate in the dilatation of the ventricle. This was due to marked thickening and

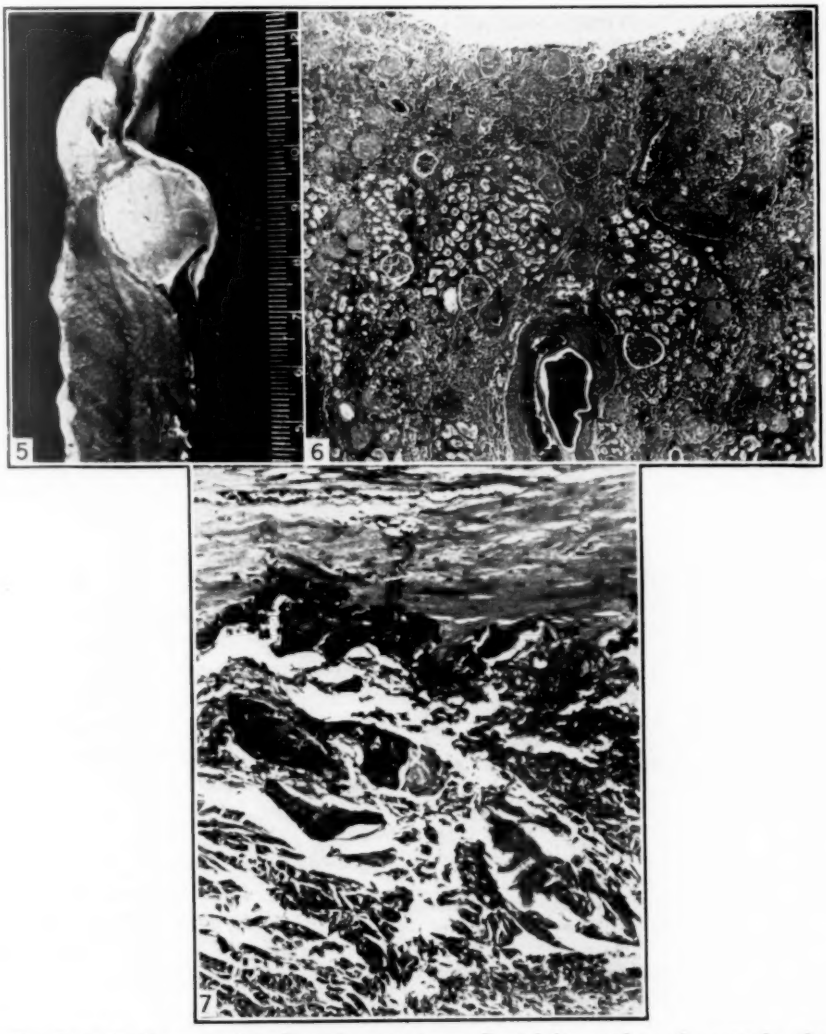

FIG. 5. CASE 3. Cross section through posterior wall of left auricle and ventricle, showing atheromatous mass arising from the mitral valve ring and pushing the posterior cusp into the ventricular lumen.

FIG. 6. CASE 3. Jagged basophilic fragment similar to the ones in the mitral ring atheroma in the wall of a large renal artery, associated with a healed infarct (x 50).

FIG. 7. CASE 3. Microscopic view of the margin of the mitral valve ring showing the fibrocalcific capsule and atheromatous material with large jagged fragments (x 150).

sclerosis of the mitral valve ring, which caused a 15 mm. bulge on the undersurface of the posterior mitral cusp. The lateral margins of this bulging mass fused with the sclerotic mitral ring. On cross section this mass was calcified in the periphery and contained yellowish-white grumous material (Fig. 5). No mural thrombi were found in the heart. The coronary vessels and the aorta showed marked atherosclerosis. No scars were noted in the spleen or pancreas at the time of the gross examination. The kidneys weighed 185 and 210 gm., were reddish-brown and their capsules stripped readily. The exposed surface was finely granular with numerous coarse depressed red scars varying from several millimeters to 1 cm. in diameter. These scars were mainly localized along the convexity of the organ giving the typical appearance of a senile arteriosclerotic kidney.

Histological examination however showed a large branch of a renal artery leading into a deep cortical scar to be almost occluded by a basophilic, jagged fragment the nature of which could not be ascertained at first (Fig. 6). Similar fragments were seen in other branches of the renal artery and in arteries of the pancreas and spleen. Invariably the fragments were embedded within the arterial wall and separated from the lumen by a layer of intima of variable thickness. This was observed in serial sections and presented also an unexpected finding. Occasionally these jagged fragments were eosinophilic.

Microscopic study of the section of the mitral valve ring clarified the nature and probable origin of the aforementioned fragments. The large atheromatous thickening of the valve ring contained fragments which were identical in size, shape and staining characteristics with the ones found in kidney, spleen and pancreas (Fig. 7). It was then decided that the lesions in kidney, spleen and pancreas were of an embolic nature. Although similar fragments may be found in aortic atheromata, the absence of the cholesterol crystals in the embolic lesions and in the mitral valve ring lesion speak against an aortic origin of the embolic material.

Closer scrutiny of the mitral ring lesion shows how attenuated the tissue is in places. One can well imagine that a lesion of this unusual size may thus perforate and empty some of its contents into the systemic circulation. The peculiar position of the embolic material within the wall of the arteries and separated from the lumen is, in our opinion, due to the lesion being healed after embolic material has become impacted in the wall, a process which in other instances led to the formation of aneurysms; for example, in healed subacute bacterial endocarditis[6].

This patient then represents a case of embolization with material from an unusually large arteriosclerotic valve ring. To our knowledge no similar case has been reported. The gangrenous toe could not be examined microscopically and might have been of embolic origin, although this is not too likely because of absence of acute embolic lesions in other organs.

Discussion. Panum[9], in a study on embolism, reported the gross findings of the autopsy of Thorwaldsen and ascribed his sudden death to atheromatous rupture in the coronary artery with occlusion due to this rupture. No microscopic examination is recorded.

Doch[4] reported a case of ruptured coronary atheroma with multiple emboli in the larger coronary branches due to cholesterol. There is no microscopic description of the lesions.

Le Count[7] describes calcareous emboli of several organs and the heart and traces these emboli back to atheromata.

Allbutt[1] also mentioned the possibility of embolization from atheromatous ulcers into various organs, making special reference to syphilitic arteritis.

Benson[2] reviewed the literature of aortic atheromata giving rise to emboli and comes to the conclusion that there is reason to believe that they are more common than had been realized.

Flory[5] is the first to describe in detail the microscopic lesions and interpret them as cholesterol emboli. He found these in the lumina of arteries of the kidney, spleen, pancreas and thyroid. Foreign body giant cells partly surround the acicular spaces. Flory found these lesions in arteries from 55 to 900μ in external diameter. In these lesions the intima was found to be hyperplastic and giant cells are an almost constant associated finding. Occasionally there were hemosiderin-filled macrophages found in the luminal occlusion, suggesting an organizing embolus or previous hemorrhage. To confirm the impression that these lesions were embolic, orig-

nating in aortic atheromata, this author scraped yellow material from several fresh aortic plaques and suspended the scrapings in physiologic saline solution. Microscopically, this suspension contained cholesterol crystals, fat droplets and red blood cells. This material was injected into the ear veins of 2 rabbits, and lesions similar to the ones described above were found in the small arteries of the lungs, surrounded by leukocytes if the animal was sacrificed 24 hours after injection, and surrounded by foreign body giant cells and hyperplastic intima when sacrificed 7 days after injection. In a review of autopsy material of 267 subjects likely to have similar lesions, he found an incidence of 3.4%. Excellent illustrations are included in this paper.

Meyer[8] described in detail 2 cases of cholesterol embolization. One case showed numerous lesions in the kidneys and in the pia-arachnoid, presumably arising from aortic atheromata superimposed on a syphilitic aortitis. The other case showed numerous lesions in the kidneys, spleen, brain, gastrointestinal tract and some in the myocardial arteries in the presence of moderately severe ulcerating atheromatosis of the aorta. The lesions he describes and illustrates are essentially similar to those described by Flory.

The findings in our 3 cases represent various aspects—some of them new—of embolization with material from atheroma. Their special features were discussed above.

Summary. 1. Embolization with atheromatous material is far more frequent than generally assumed. The pathologist usually sees the late or healed form which was described recently by Flory and independently by Meyer. Our first case belongs to this group.

2. The embolic material does not necessarily come from aortic atheroma but may occasionally arise in a systemic artery (coronary artery, Case 2) or even in an atheromatous valve ring (Case 3).

3. The acute phase of this process may represent itself as a panarteritis with many eosinophils, necessitating serial sections for elucidation of its true nature (Case 2). Foreign body giant cell formation and intimal thickening are later phases of this process.

4. Scars, *e.g.*, in the kidneys, may be caused by these emboli and microscopic scarring of the myocardium likewise.

5. Embolization with atheroma material should be regarded by the clinician as an existing and not too rare entity. Pathologists and neuropathologists should prove its presence in any given case. It is possible that a good number of cases of cerebral damage may be caused by this type of embolization, as may be transient and permanent impairment of visceral or peripheral circulation (toes, and so on).

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THE OCCURRENCE OF CHRONIC CYANOSIS IN CASES OF ATRIAL SEPTAL DEFECT

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Roesler[20], Bedford, Pap and Parkinson[4], and Burrett and White[6] presented excellent reviews of clinical and pathologic features of atrial septal defect, which is thus one of the best known syndromes in congenital heart disease. Atrial septal defect was classified by Abbott[1] and others as a late cyanotic lesion, one associated with "cyanose tardive"[3], terminal cyanosis due to a reversal of the direction of the intracardiac shunt which occurs with cardiac failure increasing pressure in the right auricle. Taussig[23] stated recently that slight acrocyanosis due to diminished blood volume and increased utilization of oxygen in the body may be present in atrial septal defect, but "there is . . . never the intense cyanosis and concomitant clubbing which are so characteristic of a venous-arterial shunt". She states that if clubbing is present it is indicative of some additional factor.

Recent studies of arterial oxygen saturation in cases of atrial septal defect[5,11,14,25] have demonstrated varying degrees of arterial anoxemia in patients who apparently were not in cardiac failure. We were provided with the opportunity of observing a patient who showed chronic cyanosis, polycythemia and clubbing of digits and who at autopsy was found to have an uncomplicated atrial septal defect. The purpose of this communication is to report this case, to review autopsied cases of atrial septal defect collected from the literature in which chronic cyanosis was observed and to discuss the possible causes of cyanosis associated with this lesion.

Case report. A 35 year old college instructor entered Stanford University Hospitals for a diagnostic checkup on May 21, 1947.

He was born at term and was not a "blue baby". Except for a slight tendency to breathlessness, his development was normal. At the age of 12, after a foot race he suddenly became extremely dyspneic and consulted a physician who told him he had a "leaky valve" and restricted his activities. At the age of 24 he developed attacks of squeezing precordial pain of 1 to 2 hours duration usually related to emotional upsets. He was not reported then as being definitely cyanotic. In his late twenties he developed clubbing of fingers. He was in reasonably good health and was moderately active, suffering from exertional dyspnea and attacks of precordial pain which were relieved by nitroglycerin. His hospitalization was prompted by a desire to find out whether his cardiac disease was correctible by surgery.

Phusical examination revealed a tall, well nourished and developed man who showed moderate cyanosis. His heart was slightly enlarged to the left. There was a diastolic shock felt. A loud second sound was heard over the pulmonic area, but otherwise no abnormal auscultatory findings were reported. After exercise there was a grade I blowing apical systolic murmur. Fingers and toes showed marked clubbing and cyanosis of the nail beds. His blood pressure was normal.

Laboratory procedures. Blood count: Hgb. 20.7 gm., rbc. 7.2 mil., packed cell volume, 58%, otherwise normal findings. Urinalysis

not remarkable. Circulation time (arm to tongue) 21 secs.; venous pressure, 7 cm. water; vital capacity, 3.4 liters. A 4 lead electrocardiogram showed right-axis deviation with diphasic T-waves in Leads 2 and 3. Oxygen saturation of venous blood was determined after immersion of the hand in warm water to approximate arterial oxygen saturation and a value of 44% was obtained.

Roentgen-ray studies. Chest roentgenograms revealed a striking prominence in the region of the pulmonary artery and its branches with widening of the upper mediastinal shadow, but only a moderate cardiac enlargement

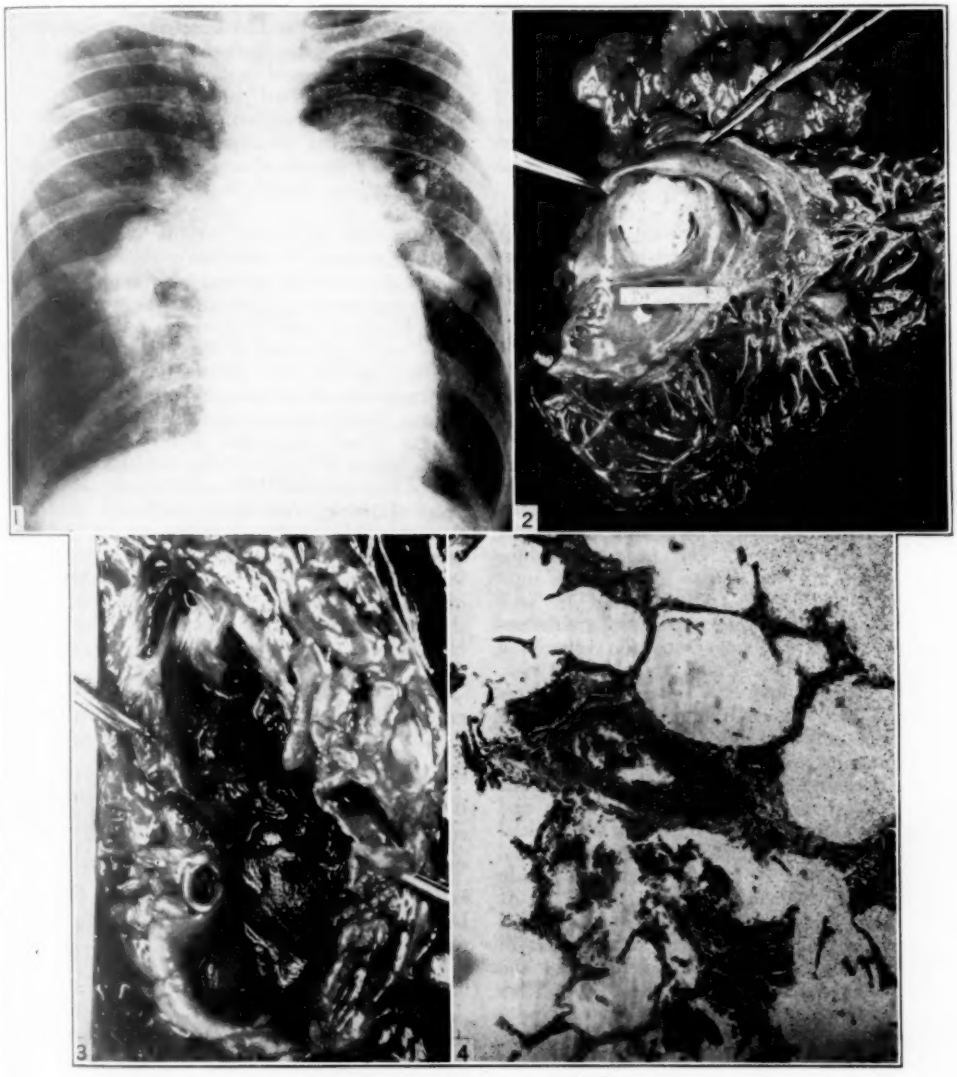

Fig. 1. Roentgenogram of chest.

Fig. 2. Right ventricle and auricle, showing hypertrophy and dilatation of the right ventricle, dilatation of the right auricle and the defect in the atrial septum.

Fig. 3. The aneurysmal sac of the left branch of the pulmonary artery, lined with thrombi.

Fig. 4. A section through the lungs showing a representative small branch of the pulmonary artery: slight medial hypertrophy and intimal thickening but no proliferative changes.

(Fig. 1). The pulsations of the pulmonary artery segment were not considered abnormal.

Course. The patient was discharged after a week's stay in the hospital and he returned to work. In December of 1947 he was examined in the out-patient clinic, and his condition was reported essentially unchanged except that a definite systolic murmur was heard along the left sternal border and his packed cell volume was 61%.

The patient was readmitted on June 7, 1948, stating that 2 days previously he had developed anterior chest pain and had had repeated small hemoptyses. Immediately after admission he complained of increasing chest pain, began expectorating blood, went into shock and died 1 hour after admission.

Autopsy. At post-mortem examination clubbing of the fingers and toes was noted. There was marked lividity of the dependent parts but no ankle or sacral edema. When the thorax was opened approximately 1 liter of clotted and liquid blood was found in the left cavity, while the right side was almost dry. The pericardial space was obliterated by diffuse fibrous adhesions. The heart, emptied of blood, weighed 525 gm. The right atrium was voluminous and almost continuous with the small left atrium through a defect about 4 cm. in diameter (Fig. 2). The remnants of the interatrial septum were represented by a blunt low ridge of tissues on the inferior margin of the defect, lying near the midline above the interventricular septum. The right ventricle had thick trabeculations; its wall was about 5 mm. thick and its chamber appeared to have about twice the volume of that of the left ventricle which was 8 mm. thick. The pulmonary valve leaflets were normal but the circumference of the valve was 11.5 cm. The following additional measurements of valve circumference were obtained; tricuspid 15 cm., mitral 12 cm., aortic 9 cm. The coronary vessels were open and free of sclerosis. The pulmonary artery and its left primary branch had a large aneurysmal dilatation about 10 cm. in diameter partially filled with layers of thrombus (Fig. 3). At the distal margin of this aneurysm there was a tear opening upon a large friable mass of clotted blood which replaced much of the pulmonary parenchyma of the left lung. This mass extended out into the pleural space through a tear in the pleura near the base. There was some old dense, white scar tissue in the region of this tear. The right primary branch was dilated but contained scattered atheromatous plaques in its wall. The left lung, which was filled with blood, weighed 700 gm.; it showed little crepitation and with pressure its cut surface exuded large quantities of blood. The trachea and both bronchi contained some clotted and fluid blood. The remaining viscera were not remarkable.

Microscopic examination. There was some thickening of the myocardial fibers of the right ventricle and the epicardial fat was replaced by loose fibrous tissue in all sections. In sections of the aneurysm the clot was composed of concentric laminae of thrombus in various stages of hyalinization. There were capillary ingrowths and numerous leukocytes in portions of the thrombus near the wall. The adjacent vessel wall was flattened and contained occasional prominent strands of collagen among the elastic fibers of the media. In the region of the rupture the fibers of the wall were fragmented and the adventitia was heavily infiltrated with leukocytes. Sections of the right pulmonary artery revealed some atheromatous thickening in the vessel walls. The pulmonary parenchyma adjacent to the tear was almost obliterated by recent hemorrhage and the more distant alveoli were filled with blood. Scattered throughout both lungs were occasional areas of old and recent focal hemorrhage. In some of the foci the parenchyma was replaced by granulation tissue containing many macrophages filled with hemosiderin. There were also a few areas with dense bands of fibrous tissue containing clusters of hemosiderin-filled macrophages. In sections of the grossly noted thickened pleura there was dense fibrous tissue containing a few aggregates of lymphocytes and occasional leukocytes. The small arteries and arterioles of the lungs were carefully inspected and showed slight intimal thickening (Fig. 4). No thrombi were found.

Comment. This is an instance of congenital heart disease with atrial septal defect in which the dilatation of the pulmonary artery assumed aneurysmal proportions and the vessel finally ruptured. Pulmonary artery aneurysms occur not infrequently in association with atrial septal defects and other lesions causing large arteriovenous blood shunts, but rupture of such aneurysms is very rare.

Clinically, this patient fulfilled most of the criteria for the diagnosis of atrial septal defect except for the occurrence of chronic cyanosis, clubbing of digits and polycythemia. These features appear to have developed during the last 10 years of life and were progressive. At no time was there any evidence

of cardiac failure, and the patient was moderately active until shortly before his death.

Pathologic features of this case were in accord with the concept of a sizable left-to-right blood shunt: dilated right auricle and a small left auricle; hypertrophy and dilatation of the right ventricle but none of the left ventricle; finally dilatation of the pulmonary artery. It is noteworthy, however, that although there were atheromatous changes in large pulmonary vessels, there were none of the obliterative changes in the small pulmonary arteries and arterioles usually associated with chronic pulmonary hypertension.

Cases collected from the literature. A group of 180 cases of proven atrial septal defect with or without concomitant mitral stenosis (Lutembacher syndrome) were reviewed. These were taken from the following sources: Abbott's[1] chart contained 73 such cases; Roesler's[20] review presented 62 cases, 37 of which were not duplicates of Abbott's cases. McGinn and White[17] reviewed 24 cases of the Lutembacher syndrome, and 7 of these were not included in previously named series. Burdett and White[6] presented a review of 31 recent cases. Welch and Kinney[28] 25 cases, and Dry[12] 4 cases. Three other case reports were used[18,21,26]. Of these 180 cases, 11 were thought to represent atrial septal defect with chronic cyanosis. These cases were accepted in the presence of a history or observation of longstanding cyanosis and one or both of objective confirmatory signs: clubbing and polycythemia. The pertinent pathologic findings in these 11 cases and in our case are presented in Table 1.

It is shown that cyanosis was present since birth in 2 cases and in the majority of others it appeared in the second decade of life. Cyanosis was described in most cases as moderate, in some as severe. Clubbing was present in all cases except one. Polycythemia was reported in 7 of the 8 cases in which blood counts were recorded. Eight patients died of heart failure, 3 from other causes.

The heart was reported as enlarged in all but one case. In most cases severe hypertrophy was present, usually limited to the right ventricle. The defects varied from moderate sized ones to an almost complete absence of the atrial septum. In 2 cases multiple defects were reported. There was no uniformity in the location of the defects. Some were reported as widely patent foramen ovale, others as persistent foramen primum. In cases with very large defects, identifying landmarks in the atrial septum were obliterated. In 11 cases description of the pulmonary artery was available: it was reported as small in 1, normal sized in 3, moderately dilated in 2 and of aneurysmal proportions in 5. Complicating mitral stenosis, apparently rheumatic in origin, was recorded in 3 cases. In 1 of them the degree of mitral stenosis was probably severe enough to have affected hemodynamics, in the other 2 it was mild.

The sex incidence in this series was: males 8, females 4. The youngest patient was 16, the oldest 44 years of age.

Discussion. It is shown beyond any doubt that cyanosis not related to cardiac failure may occur in cases of atrial septal defect with or without complicating mitral stenosis. The degree of cyanosis and of the accompanying polycythemia and clubbing, and the age of their onset, places some of these cases very definitely in the cyanotic group of congenital heart disease. They constitute only a small fraction of the total number: 7% of the reported cases exhibited definite chronic cyanosis.

The fact that atrial septal defect may take the form of morbus caeruleus introduces a new problem in the differ-

TABLE 1.--FINDINGS IN 12 CASES OF ATRIAL SEPTAL DEFECT WITH CHRONIC CYANOSIS

Author, year	Age, sex	Cyanosis	Clubbing	Polycythemia	Cause of death	Heart weight (grams)	Atrial septal defect:	Pulm Art.:	R.V.:	Other findings
Johnson 1878	35 M	since birth +++	++			600 gm.	open F.O., 4-5 cm diam.	norm. size	+++	
Sundberg 1905	22 M	since adolescence ++	+		heart failure		2 defects, large poster., small anterior	dilated	+++	small aorta
Cabot 1926	24 F	? 4 years duration ++	+		heart failure	665 gm.	widely open F.O. (1½ cm diam.) ant. defect, 1 cm.	dilated 2x size of aorta	++	small aorta mild mitral stenosis
Zadoc-Kahn 1926	30 M	for at least 2 years +++	since childhood ++	+	heart failure	450 gm.	atrial septum almost completely absent			
Wahl 1931	21 F	at 17 + later ++	+	+	operation	625 gm.	widely open F.O. 22 mm in diam.	aneurysmal	+++	small aorta
Okkels 1932	31 M	since 16 ++	+	++	heart failure	775 gm.	fossa ovalis perforated by mult. defects, total size: 2 cm diam.	aneurysmal dilatation	+	
Costa, 1931	16 F	since 14 ++ terminally +++	+		heart failure	large	poster. to F.O. mult. holes: 1 cm; 1x2 cm and 4 mm in diam.	small	+	
Bedford 1941	44 M	since 25 ++	++	+	heart failure	large	F.O. closed, below it oval defect 2x3.5 cm	aneurysmal dilatation	+++	
Bedford 1941	33 M	since birth +++	++	++	heart failure	930 gm.	large aperture in position of F.O. 2 x 3 cm.	normal	+	mitral stenosis, calcar., severe
Massee 1947	39 M	++		+	heart failure	640 gm.	F.O. closed, open septum primum 5 x 5 cm	twice normal size	+++	fibrosis of mitral & tricus. valves; mild mitral sten.
Gates 1947	39 F	cyanotic at 19 +++	++		cereb abscess	310 gm.	widely open F.O. 3 x 2.5 cm		++	
Authors' case	36 M	developed in mid-twenties ++	++	++	rupture of pulm.art. aneurysm	525 gm.	large defect (4 cc diam.) most of atrial septum absent	aneurysmal dilatation	++	

LEGEND:
R.V. - right ventricle; F.O. - foramen ovale; + - slight; ++ - moderate; +++ - severe (in column: "R.V." degree of hypertrophy).

ential diagnosis of congenital heart disease. Our case illustrates the similarity between the Eisenmenger complex and the cyanotic form of atrial septal defect. In both of these conditions roentgenographic and electrocardiographic findings are identical, and even physical findings bear a close resemblance in that systolic murmurs located in the apical area and the lower left sternal border occur in both syndromes, and early diastolic pulmonary murmurs may be present in either case. With cyanosis, moderate in degree, appearing in late childhood, differential diagnosis between the Eisenmenger complex and the atrial septal defects may be impossible by ordinary means and may have to rest entirely upon the result of venous catheterization of the heart.

In addition to the diagnostic difficulty this problem calls for an answer to a fundamental question, which we shall attempt to discuss: Is cyanosis associated with atrial septal defect due to the congenital defect itself, or to complicating and secondary factors?

Since Lundgaard and VanSlyke's[16] studies and Abbott's[1] application of their principles to congenital heart disease, venous arterial blood shunt was regarded as the main cause of chronic cyanosis in congenital morbus caeruleus. In the recent years another mechanism has been suggested in some cases of congenital heart disease: Burwell[7] and then Taussig and Blalock[24] thought that in the Eisenmenger complex incomplete oxygenation of the blood in the lungs may be responsible for arterial anoxemia. Brannon, Weens and Warren[5], and Massee[18] thought that obstructive pulmonary disease and difficulty in oxygen diffusion in the lungs were responsible for arterial anoxemia in their case of atrial septal defect associated with cyanosis. This was based on the fact that in it the right ventricular and pulmonary arterial pressures were very high and arterial oxygen saturation rose in response to breathing of pure oxygen. In another case of atrial septal defect (not autopsied) Handelsman *et al.*[14] found lowered arterial oxygen saturation and high pulmonary arterial pressure, but interpreted their findings as indicative of a predominant right-to-left intracardiac shunt due to increased resistance of the pulmonary vascular tree. Taylor *et al.*[25] studied a group of patients with atrial septal defects clinically with the aid of venous catheterization of the heart and found occasional subnormal values of arterial oxygen saturation. These authors explain it on a basis of venous-arterial blood shunt, which, they think, may occur in a very large defect, where the 2 auricles form a common chamber.

Thus, 3 ways have been suggested in which arterial oxygen saturation could be lowered in cases of atrial septal defect. Two of them necessitate the presence of a complicating factor: pulmonary vascular sclerosis or pulmonary hypertension; the third one calls for the presence of a very large defect.

Reviewing the pathologic findings in cases of atrial septal defects with cyanosis (Table 1) and the physiologic data accumulated in the last few years by catheter studies, one can confidently dismiss the possibility that pulmonary oxygen exchange is interfered with in all such cases. Pulmonary vascular sclerosis was not a consistent finding in cyanotic cases. In our case it was specifically searched for and found not to be present. In addition, no proof has been offered that pulmonary vascular changes per se, without changes in the lungs, impede oxygen exchange. The conclusive evidence has been provided by successful determinations of the oxygen saturation of pulmonary venous blood which was found to be normal: Handelsman *et al.* reported that in 16

cases the pulmonary vein was catheterized and the blood was fully saturated with oxygen. Details were not given and it is not known whether some of these cases were cyanotic. More significant are cases reported by Dexter *et al.*[11] and Taylor *et al.*[25], each of whom reported 1 case in which arterial anoxemia was present but the blood returning from the lungs was fully saturated with oxygen. Until and unless conclusive evidence is presented that pulmonary venous blood may be anoxemic, pulmonary factors in the production of cyanosis in atrial septal defects can be dismissed and intracardiac shunt can be taken to be the sole cause of anoxemia.

The second possibility, that pressure relationships cause a predominantly right-to-left interauricular shunt, does not fit in with the clinical facts and the postmortem findings. Handelsman *et al.*[14] based their views on a clinically studied case in which the calculated systemic flow was 4 times larger than the pulmonary blood flow. If these calculations were correct, this case would most likely be an exception rather than an average case, as the intense pulmonary congestion usually noted during life, the postmortem findings of a large right auricle, the small left auricle, the dilatation of the right ventricle and pulmonary artery, the small aorta are all incompatible with a large systemic and small pulmonary blood flow. Also, similar calculations by other authors[11,25] have shown the systemic flow to be smaller than the pulmonary flow even in the presence of arterial anoxemia.

Clinical and pathologic findings in cases of atrial septal defect with chronic cyanosis show the same indirect evidence of a large venous-arterial blood shunt as in cases without cyanosis. Such findings speak strongly against the possibility that pulmonary arterial sclerosis or other factors lead to a permanent overall right-to-left shunt in cyanotic cases. In cases of atrial septal defect the pressure in the left auricle is higher than in the right[10]. It is not known whether this relationship is reversed in the presence of high right ventricular pressure unless right ventricular failure with diastolic hypertension ensues. It should be noted that in the Lutembacher syndrome, the addition of mitral stenosis would accentuate the left-to-right shunt, and yet chronic cyanosis may occur in such cases as well as in uncomplicated atrial septal defects. All these arguments make a change in pressure relationship between the auricles and a resulting permanent overall right-to-left shunt very unlikely.

The possibility of free mixture of venous and arterial blood in cases where both auricles would form a single functional chamber seems to offer the best explanation for cyanosis associated with very large atrial septal defects. In such a case venous blood from the systemic circulation and fully oxygenated pulmonary venous blood could mix freely and the oxygen saturation of this mixture would lie between the values of the arterial and the venous blood. This mixed blood would then flow into both ventricles and gravity[26] or higher pressure on the left side could force more of it into the right heart than the left, causing unequal outputs of the 2 ventricles. The free mixing of blood in a single auricle could, but need not, take place in every case since most of the blood could follow the normal direction even with an absent septum, and mixing could be minimal.

Free mixing of blood in cases of a complete or almost complete absence of the atrial septum offers an explanation of cyanosis consistent with cardiodynamics on one hand and with the pathologic relationship of the ventricles and great vessels as found in these cases on the other hand. A disturbing fact, however, is that in this series

there is no uniformity in the presence of very large septal defects: only one case was actually reported as a "trilocular heart"[29] with a single auricle, and of the remainder, our case and 3 others could be regarded as very large defects. The rest should be classified as moderate sized defects, single or multiple. One is impressed by the fact that the gross pathologic findings in the 12 cyanotic cases, especially the size and location of the defects, present a good cross section of the 180 cases of atrial septal defect.

Another possible mechanism of cyanosis has occurred to us, namely a directional flow of venous blood into the left auricle. If proper anatomic conditions existed, namely a certain relationship of one of the venae cavae to the septal defect, one could visualize a stream of blood thrown directly into the left auricle during the part of the cycle when pressure differences between auricles are smallest. This need not interfere with the large left-to-right shunt during the remainder of the cardiac cycle. The occurrence of such streamlining of blood in the fetal circulation has recently been reaffirmed[2]: in the fetus such a mechanism causes the reverse, namely oxygenated blood from the placenta arriving through the inferior vena cava is shunted directly into the greater circulation.

The possibility of a streamline blood shunt in atrial septal defect is speculative but attractive, as it would best explain apparent inconsistency between the presence of venous blood in the greater circulation and a large left-to-right interauricular blood shunt in cases where free mixture would not appear likely because of the modest size of the opening. Since such a mechanism would be caused by an anatomic chance it would explain the occurrence of cyanosis in some cases and its absence in others, and the lack of correlation between the presence of chronic cyanosis and the gross anatomic findings.

Since cyanosis, clubbing and polycythemia are clinical manifestations of higher degrees of arterial anoxemia, one might ask whether arterial anoxemia insufficient to cause visible cyanosis is a common or constant feature of atrial septal defect. The answer is provided in the reports of arterial oxygen saturation values in cases diagnosed by venous catheterization of the heart. Such readings are reported in 17 cases[5,11,14,25]: in 5, normal values were found (saturation of 95% or more); in 9, minimal anoxemia was present (values between 88% and 95%), and 3 patients had definitely anoxemic values: 79%, 70%, and 67% respectively. These findings indicate that small quantities of venous blood frequently enter the left auricle, and in a small proportion of cases large quantities find their way into the greater circulation.

Summary and Conclusions. 1. A case is presented of a large atrial septal defect in a 35 year old man who showed the triad of chronic cyanosis, polycythemia and clubbing of the digits, and who died of rupture of an aneurysm of the pulmonary artery without ever exhibiting evidence of cardiac failure.

2. A review of 180 proven cases of atrial septal defects with or without concomitant mitral stenosis reported in the literature showed that in 11 patients persistent and longstanding cyanosis not associated with cardiac failure was present.

3. Pathologic findings in these cases did not differ from those in other, noncyanotic cases. Large defects involving most of the atrial septum were common among cyanotic cases but there was no apparent relationship between the size of the defect and the presence of cyanosis.

4. The pathogenesis of cyanosis

associated with atrial septal defects is discussed. Deficient pulmonary oxygenation is not regarded as a likely factor in the production of cyanosis, nor is a changed pressure relationship in the auricles leading to a persistent venous-arterial blood shunt. With the clinical and pathologic evidence pointing to a large volume of blood being shunted from the left to the right auricle, the most likely cause of cyanosis appears to be a free mixing of blood in very large septal defects and, or, anatomic conditions permitting a stream of venous blood from the great veins to enter the left auricle directly.

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A STUDY OF 22 CASES OF CARRION'S DISEASE WITH INTERCURRENT MALARIA*

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In the last century before the etiologic agents of malaria and Carrion's disease were known, many interesting associations were noted between the 2 diseases. In 1887 Tupper[15] found that Verruga Peruviana was present in an area where malaria was also endemic and unfortunately many persons contracted both diseases. Carrion[8] noted that the geographical distribution was similar but pointed out that malaria and Verruga Peruviana occur independently of each other but can coexist in the same person. Dounon[3] concluded that the 2 diseases had a similar pathogenesis and Odriozola[11] found that similar conditions were necessary for the life of the etiologic agents in these diseases. Garcia-Merino[4] correlated the presence of flood waters with the onset of epidemics of Carrion's disease. Today it is known that both diseases are transmitted by mosquitoes: malaria by Anopheles and Carrion's disease by the phlebotomus[6].

The present report is a study of the relationship between Carrion's disease and malaria, as observed in a group of 22 cases found to have both diseases.

Malaria parasites were found in smears of the peripheral blood in all of the 22 cases of this series. The type of plasmodia were: *P. vivax* in 18, *P. falciparum* in 2, and *P. malariae* in 2 cases. In 3 patients the malaria parasites were demonstrated in the peripheral blood following *Bartonella bacilliformis* anemia, hereafter, B.b.a. (Oroya Fever), in another 3 during the preeruptive stage, and in 16 during the eruptive stage of the bartonellosis with verrugae in the skin.

Malaria and Carrion's disease may be contracted at the same time or one may precede the other. Patients with severe B.b.a. which were followed by malaria showed clinical features which were atypical for both diseases. The fever was irregular and without the characteristic periodicity of malaria, there was profuse sweating, enlargement of the spleen, and frequently a macrocytic or normocytic normochromic anemia with monocytosis varying from 8 to 20%. These symptoms and signs do not occur in uncomplicated cases of B.b.a.

When malaria was contracted during the eruptive phase of the verrugae, the malarial seizures were usually typical and easily recognizable with chills, high fever and sweating occurring periodically every day, or every second or third day. The morphological aspect of the verrugae changed rather suddenly, they lost their turgescent appearance and disappeared rapidly. Other verrugae assumed a dark violaceous color from thrombosis or hemorrhage. The pains in the bones and joints which were usually present during the preeruptive stage and disappeared with the eruption of verrugae again reappeared. The hematological findings in cases with malaria during the eruptive stage of Carrion's disease were quite

* This study was made in Lima, Peru, from 1938-1943 at five different hospitals: Dos de Mayo, Arzobispo Loaiza, San Bartolome, Del Nino, and Maternidad.

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typical of malaria without any features of B.b.a. In this series of 22 cases with both diseases, monocytosis was found in every one and splenomegaly in 20 cases (91%).

Report of Cases. The following 2 cases illustrate malarial seizures during the eruptive stage of Carrion's disease.

CASE 1. E. R., a 28 year old, single, Peruvian soldier, had malaria for many years with the last seizure in 1935. In February of 1941 he was sent to an area where Carrion's disease is endemic. In the 3rd week of February he developed malaise with a fever fluctuating between 38° and 39° C., anemia and slight icterus of the skin and sclera, dizziness, cramps in the epigastrium, nausea and occasional vomiting. In the first week of March the fever gradually disappeared, his appetite improved and for the first time he experienced pain in the various bones and joints. This episode apparently corresponded to a B.b.a. On March 19th the patient experienced a chill followed by a fever lasting a few hours, profuse sweating and vomiting. This symptomatology recurred twice every other day at the same hour of the day and disappeared after intensive antimalarial treatment with quinine. Red pointed cutaneous nodules then appeared and the pains in the bones and joints of the feet became so intense that hospitalization became necessary on May 30th, 1941. The patient appeared as a well-developed but emaciated man with slight anemia, a soft non-transmitted systolic murmur at the apex of the heart and an enlarged hard spleen extending to the level of the umbilicus. Many red nodules in regression were present, especially on the lateral surfaces of the legs. The urine examination was negative and no parasites could be found in the stools. The erythrocytes were 3.3 million per c. mm., 7700 leukocytes (48% granulocytes, 10% monocytes, 42% lymphocytes). No malaria parasites were found. Analgesics were given and the patient remained afebrile during the first week of hospitalization. On June 1st he was seized by a chill followed by fever and profuse sweating: this recurred on the 6th of June and on that day *P. vivax* was demonstrated. After antimalarial treatment, the patient remained afebrile until his discharge on the 30th of June. The red cell count increased to 3.8 million per c. mm. and the size of the spleen was unchanged.

CASE 2. B. C., a 34 year old, single, male had experienced several episodes of malaria in the preceding 7 years. In April 1941 he remained for 2 months in an area where both Carrion's disease and malaria are endemic. On the 20th of June he developed chills followed by fever, which recurred the following morning at the same hour. Despite quinine medication the fever continued, anemia and slight icterus developed and the pain in the bones became quite intense. He also had migratory pains in the joints of the left wrist, elbows and feet and when they were located in the maxilla they were so severe as to make it impossible for him to masticate food. Pain was also present in the left upper quadrant of the abdomen and he was told that he had a "big spleen". In the first week of August, edema of the lower extremities was noticed. On admission on August 20th, 1941, he appeared well developed, undernourished, with marked anemia and pallor of the skin, and a heart normal in size with soft and non-propagated hemic murmurs. The spleen reached the level of the umbilicus in the left mid-clavicular line. A few small lymph nodes, the size of a pea, were noted in the neck, axilla, epitrochlear and inguinal regions. Urine examination was normal. The erythrocyte count was 3.82 million per c. mm.; 8000 leukocytes (56% granulocytes, 1% eosinophils, 18% monocytes and 25% lymphocytes). The fever continued to fluctuate between 37° and 38° C. for nearly a month and then subsided. The pains in the bones and the joints persisted but finally disappeared altogether on the 22nd of October. A few pinpoint verrugae became visible and rapidly increased in size, the anemia improved markedly, the pains faded away and the patient was discharged on the 15th of November, 1941, in very good general condition. Approximately one week after his discharge the chills and fever recurred, the pains in the bones and joints reappeared and a marked involution and disappearance of many of the verrugae was noted. *P. vivax* was found in the smears of the peripheral blood. Quinine was again given with disappearance of the malarial manifestations. The spleen decreased only slightly in size.

It is possible that this patient contracted malaria and Carrion's disease at the same time. The verrugae regressed rapidly after a recurrence of vivax malaria.

CASE 3. V. C., a 17 year old Indian farm-worker who had lived all of his life in the high mountains of Peru, in December of 1939 visited an area where Carrion's disease is endemic. Two months later he was suddenly seized with a chill which was followed

by fever. The chills did not recur but the fever was continuous for nearly one month. The patient became pale and anemic with extreme malaise, dyspnea on effort and anorexia; quinine was given without any improvement. He then moved to an area where Carrion's disease does not exist but where malaria is endemic, and here he promptly recovered.

In August, 1940, he noticed several red points in the skin which grew to the size of a pea, representing the eruptive stage of Carrion's disease. In the 2nd week of August chills occurred every day at noon, followed by high fever which lasted only a few hours, profuse sweating, anemia, cough and mucopurulent expectoration. The patient came to the Dos de Mayo hospital in Lima on September 2nd. He appeared to be a well-developed, well-nourished pale young man with profuse sweating and murmurs noted at the apex of the heart and with an enlarged spleen reaching almost to the umbilicus. Verrugae of pinpoint to pea size were distributed irregularly over the skin, but mainly on the lateral surfaces of the legs, most of them in regression. There were also several round hyperpigmented areas, 1 cm. in size, corresponding to the locations of previously implanted verrugae. The urine examination was normal. Blood counts: 2 million erythrocytes per c. mm., 8300 leukocytes, 12.6 gm. hemoglobin, and 28.35 hematocrit. The differential count showed 35% granulocytes (metamyelocytes 2%, stab cells 11% and segmented cells 22%), 3% basophils, 4% monocytes and 58% lymphocytes. *P. vivax* was demonstrated in the blood smears. Under quinine treatment the spleen decreased markedly in size and, on September 21st when the patient was discharged, it could no longer be palpated.

This case illustrates an intense anemia, resistant to quinine treatment, corresponding B.b.a. contracted 2 months earlier while in an area where Carrion's disease is endemic. Later during the eruptive stage of the disease the patient had a vivax malaria.

CASE 4. V. Ch., a 20 year old, single, Indian miner, came from an area where Carrion's disease and malaria are both endemic. In the second week of March, 1938 he developed malaise, loss of appetite, vomiting and a productive cough, with mucopurulent sputum. He entered the hospital on the first of April. Blood counts: (April 3rd) 2.4 million erythrocytes and 6900 white cells per c. mm. (granulocytes 43%, eosinophils 4%, monocytes 12% and lymphocytes 41%); there were 2 normoblasts per 100 leukocytes. Six weeks later the patient left the hospital markedly improved. In the 2nd week of May he noticed pains in the bones of the extremities especially in the right shoulder. Pin point verrugae in the skin was noticed the first week of June. The patient came to the hospital on the 4th of August to have a verruga of the left lower lid removed surgically. Besides these verrugae, the only abnormal finding was an enlarged spleen reaching 2 fingerbreadths below the left costal margin. The blood counts on admission were as follows: erythrocytes 5.82 million per c. mm., leukocytes 9000. On the 11th of August the patient developed suddent chills. Blood counts: 3.89 million erythrocytes per c. mm., 5900 leukocytes (65% granulocytes [14% stab cells and 51% segmented forms], 4% eosinophils, 1% basophils, 12% monocytes and 18% lymphocytes). Several ring forms of *P. falciparum* were found. The fever and other symptoms disappeared with antimalarial treatment and most of the verrugae regressed quite rapidly.

Carrion's disease and a falciparum malaria were apparently contracted at the same time by this patient. Because of his splenomegaly, profuse sweating and monocytosis, he was given quinine with remission of his fever and anemia. The diagnosis of malaria complicating Carrion's disease was later confirmed.

CASE 5. O. B., a 21 year old Peruvian, spent 4 days in the last week of April, 1941, in an area where Carrion's disease is endemic and then went to work in a place where malaria is endemic. On June 7th, 1941, he noticed malaise and profuse sweating followed by a high and continuous fever. The patient became anemic and was bedridden in the second week of June, continuing with the high fever despite the intensive antimalarial treatment. He developed headaches and on several occasions epistaxis and bilious vomiting along with anorexia, marked polydypsia, sweating with cramps occurring in both feet. Later he became delirious, describing imaginary animals and numerous lights of different colors. The urine became very dark. There were also severe pains in the muscles of the extremities. He was hospitalized in Lima for further treatment on June 2nd, 1941, and appeared pale, undernourished, acutely ill with enlargement of the spleen 2 fingerbreadths below the costal margin. Lymph nodes the size of a pea, semi-hard and non-

tender, were palpated in the cervical, axillary, epitrochlear and inguino-crural regions. The pulse was 110, respirations 36 per minute, blood pressure 115/85. The erythrocyte count was 1.13 million per c. mm., hemoglobin 6 gm., white count 8920, reticulocytes 10.2%, and hematocrit 11.55. A few bartonellae were noted in the smears of the peripheral blood. In the next few days there was a marked clinical improvement, the temperature oscillated between 37° and 38° C., and the erythrocyte count rose. On July 10th he again developed fever preceded by chills, the erythrocyte count dropped from 2.11 to 1.7 million on July 12th, when a few ring forms of *P. vivax* were found in the blood. After intensive antimalarial treatment with quinine and atebrine the patient recovered.

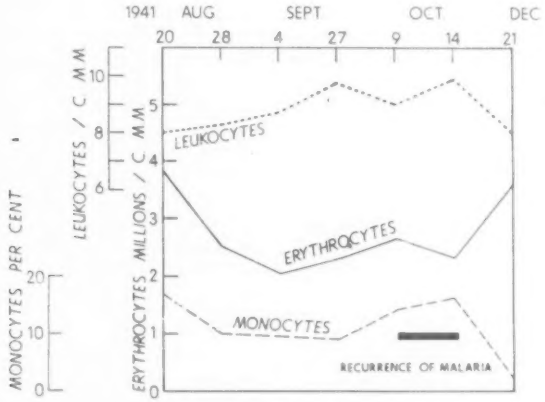

FIG. 1. Patient with erupted verrugae and anemia. The treatment of an intercurrent malaria was followed by decrease in the number of monocytes and a rise in the erythrocyte count.

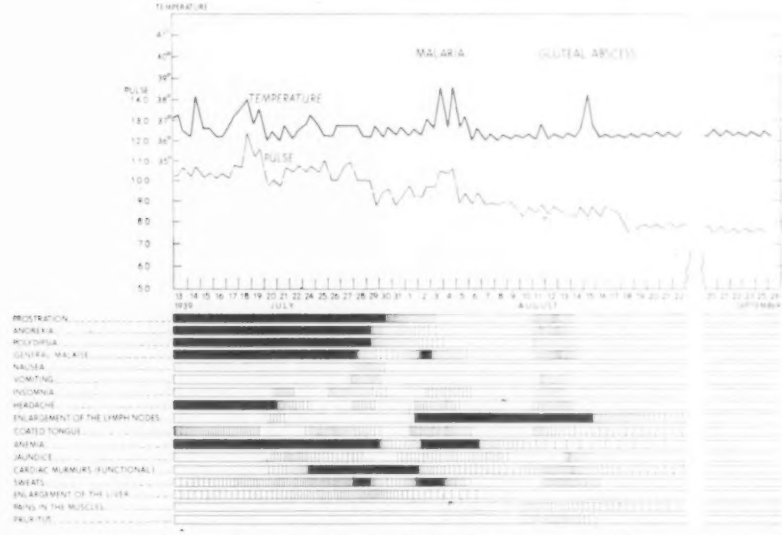

FIG. 2. Recovery phase of Bartonella bacilliformis anemia which was followed by a malaria infection. The solid lines represent a marked severity of symptoms; the light line indicates a lesser degree of severity, and the empty blocks represent an absence of symptoms. The greater the distance between lines, the less marked are the symptoms.

This case illustrates an intercurrent malaria infection which occurred shortly after the *B. bacilliformis* had disappeared from the peripheral blood.

Case 6 (Figs. 2 and 3). R. Ch., a 45 year old, single, Peruvian negro male, worked for 3 years prior to admission, in an area where Carrion's disease is endemic. On June 28th, 1939, he had a chill followed by a fever of 40.3° C. and general malaise. The chill did not recur but the fever continued. On July 4th, 1939, he was admitted to the hospital and physical examination revealed a pale, well-nourished and well-developed man with slight jaundice of the sclerae. A functional systolic murmur was heard at the apex and in the aortic areas of the heart. The liver was palpated 2 cm. below the costal margin in the right midclavicular line. The blood pressure was 120/70, pulse 108 per minute, and the respirations 17. The urine contained traces of albumin and the Wassermann and Kahn tests were negative.

The patient continued to have a slight fever until the 20th of July along with a progressive anemia which on July 23rd recorded 1.28 million red cells per c. mm. with *B. bacilliformis* in the erythrocytes. The bartonellae soon disappeared, the temperature became normal, the anemia improved and the patient developed a ravenous appetite. However, on the 1st of August he complained of headache, vomiting, profuse sweating, recurrent slight jaundice and some fever in the evening. On August 3rd, the erythrocytes numbered 2.07 million per c. mm., leukocytes 9600 (58% granulocytes [3% metamyelocytes, 18% stab cells, 37% segmented forms], 1% basophils, 18% monocytes, 23% lymphocytes). A few of the erythrocytes contained *P. vivax*. The patient was treated with 2.5 gm. of quinine daily given intramuscularly and by mouth, the erythrocyte count decreased to 1.43 million per c. mm. There was a complete remission of symptoms after this medication except for a slight elevation of temperature, on August 14th, which was attributed to local inflammation of the gluteal muscles after injection of quinine. The patient left the hospital on September 14th, 1939, with a count of 4.4 million erythrocytes, hemoglobin 15 gm. %, hematocrit 41.42%. The monocytosis disappeared after administration of quinine. Eruption of verrugae had not occurred.

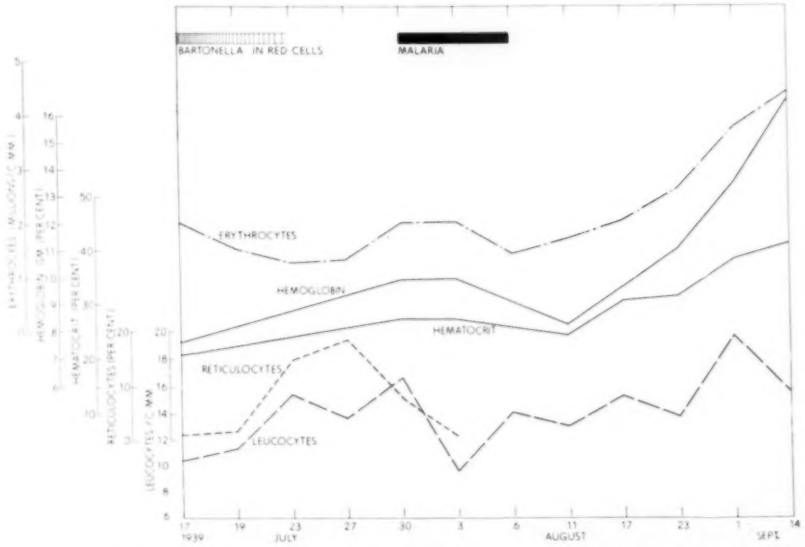

Fig. 3. Bartonella bacilliformis anemia followed by an intercurrent vivax malaria producing a transitory fall in the erythrocyte count and hemoglobin.

Discussion. Intercurrent malaria infection in Carrion's disease is a frequent rather than a rare event as might be gathered from the few isolated reports[2,5,7,9,12]. In previous studies, the author reported such intercurrent infec-

tion in over one-fourth of the hospitalized cases[13,14]. Several features of intercurrent malaria, such as intermittent or remittent fever, profuse sweating, monocytosis and splenomegaly, were originally attributed to Carrion's disease itself. In this series of 22 cases proven to have both diseases, monocytosis was found in every one and splenomegaly in 20. Arce[1] had previously emphasized that splenomegaly does not occur in uncomplicated cases of Carrion's disease.

The immunological course of Carrion's disease seemed little affected by the malaria and in several cases the bartonella disappeared from the red cells as the malaria organisms increased in number. This observation agrees with the findings of Noguchi[10] who experimentally infected monkeys with *B. bacilliformis* and *plasmodia* and found that the development of malaria during convalescence from bartonellosis did not change the course of the latter. Even the combination of splenectomy and malarial inoculation did not significantly alter the course of the experimental bartonellosis. No fatality occurred in the present series of cases with both diseases.

Summary. A study is presented of 22 cases of Carrion's disease with intercurrent malaria. In 3 of these patients who developed malaria following *B. bacilliformis* anemia (Oroya Fever) it was observed that the clinical features were atypical for both diseases. Three cases had malaria in the preeruptive stage and 16 during the eruption of verrugae. The malaria seizures in this last group were typical and easily recognizable, the verrugae rapidly regressed and disappeared. Monocytosis was found in every case of this series and splenomegaly in 20 (91%). The immunological course of Carrion's disease was little affected by the intercurrent malaria.

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METABOLIC STUDY OF GYNECOMASTIA ASSOCIATED WITH LIVER DISEASE*

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Gynecomastia is a phenomenon seen in association with many diverse and apparently unrelated diseases. It has generally been ascribed to a derangement of endocrine function involving one or several glands. The study of estrogen metabolism in association with breast enlargement has been the subject of a number of papers, but there is still some controversy as to the quantitative relationship. In addition, the correlation of liver disease and feminizing changes has attracted much interest in recent years, although it was first noted by Corda[4] in 1925.

In the present paper we shall emphasize several of the unusual features of this entire subject. We have studied a case of unilateral gynecomastia with relation to endocrine titers, liver function studies, liver biopsies, effects of administered estrogens, and relation of improvement in liver function to feminizing features, and will attempt to correlate all these findings in the following discussion so that they may serve as a basis for a clearer understanding of the problem and as a means for quantitative studies in other patients. The relation of estrogen metabolism and liver disease to gynecomastia has been repeatedly emphasized because the liver is the principal organ responsible for estrogen inactivation and conjugation.

Methods. The determination of the various endocrine titers was performed by a combination of several previously described methods as modified by Dr. G. R. Kingsley of our biochemical laboratories. The extraction and purification of the urinary estrogen was carried out by the procedure outlined by Salter[26]. The colorimetric determination of the purified estrogen was carried out according to the procedure outlined by Cohen and Bates[3]. The free estrogens were determined by extracting unhydrolyzed urine by the method of Salter. The determination of urinary pregnandiol was accomplished by our modification of the method of Goldzieher[9]. The total 17 keto-steroids were determined by a modification of the methods suggested by Dreckter[5] and Pincus[23].

Serial liver biopsy studies were made using the intercostal approach with a Vim-Silverman needle. Breast measurements were made with a flexible ruler using a central point stained with indelible dye to insure the same point of measurement each time. Testicular measurements were made with the same flexible ruler.

Case Summary. *History*: A 30 year old Mexican male was admitted to the hospital on August 25th, 1948, with a history of a running nose, headache, a productive cough with thick yellow sputum, fever, and a dull aching in the left chest region for the preceding 3 weeks. For 10 days before entry, he had noted a dull aching pain in the right upper quadrant aggravated by ingestion of food, marked weakness, the appearance of a yellow tint to the skin, golden-colored urine,

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and light-colored stools. He had had considerable nausea with occasional vomiting for several days before entry.

He gave a past history of having ingested 1 to 2 quarts of wine daily for 14 years. During this time, his diet had been very inadequate and he had not eaten at all on the days on which he was drinking heavily. A dietary analysis revealed a deficiency in total calories, all vitamins, and a low protein intake (See Table 1). The patient stated that he had noted a unilateral enlargement of his left breast, a gradual loss of pubic, chest, and axillary hair, a gradual loss of libido, and an inability to conduct intercourse satisfactorily. These symptoms had all appeared during the past 12 to 18 months and had been progressive.

Physical Examination: On entry, the patient had a temperature of 99.8°, pulse 96, and respirations 24. He was markedly icteric and appeared chronically ill. The nasal mucous membranes were markedly engorged, but the throat was relatively normal. Decreased breath sounds, increased voice sounds, and fine crepitant rales were heard in the right axillary region and in the right lung posteriorly at the base. The abdomen was somewhat distended and shifting dullness was present. The liver edge was palpable 4 finger-breadths below the right costal margin. The spleen was not palpable. The left testicle was markedly atrophic. There was a marked diminution of the axillary, chest, and pubic hair. A diffuse hypertrophy of the left breast region was noted with no abnormality of the nipples. The left breast measured 7 cm. in transverse diameter. Many spider angiomata were seen over the neck, chest, and upper extremities.

Laboratory Data: Laboratory studies are summarized in Table 2. The sedimentation rate was 25 mm. per hour. Chest Roentgen-rays revealed a homogeneous density in the apex of the right lower lobe, which was interpreted as representing pneumonia. Follow-up chest Roentgen-rays 2 weeks later revealed clearing of the pneumonic area. Liver biopsy shortly after entry revealed portal cirrhosis with conspicuous fatty changes of the liver cells (Fig. 1).

Course in Hospital: Following resolution of the pneumonic process with penicillin therapy, a number of basal determinations were made, including liver biopsy, breast size measurements, testicular measurements, complete endocrine studies, and an accurate count of both large and small spider angiomata. The patient then received amniotin (estrone in oil) in a dosage of 40,000 units intramuscularly daily for 1 week, followed by 120,000 units intramuscularly daily for an additional week. At the termination of estrogen administration, during which time the patient had no symptoms, the size of the left breast had increased slightly in diameter, no change in hair growth was noted, a liver biopsy showed improvement, liver function tests showed improvement, and the total number of angiomata had decreased. The patient had received no therapy during this time except for the regular hospital diet which was adequate in all constituents.

TABLE 1. DAILY DIET ANALYSIS

	Prior to Hospital	Regular Diet	Special Liver Therapy Diet
Protein	127 gm.	90 gm.	250 gm.
Carbohydrate	55 gm.	275 gm.	380 gm.
Fat	76 gm.	130 gm.	65 gm.
Calories	1430	2700	3100
Vitamin A	1800 I U	5000	15,000
Thiamine	.83 mg.	1.5 mg.	1.5 mg.
Riboflavin	.77 mg.	5 mg.	1.8
Ascorbic Acid	32	75	200
Niacin	8.8 mg.	12	16.5

The patient was next placed on an intensive therapeutic regime consisting of a high protein, high carbohydrate, low fat diet with protein supplements including 1 ounce of nutragest and 1 ounce of protolysate daily. He also received a vitamin B complex intramuscularly daily consisting of 10 mg. thiamine, 10 mg. riboflavin, 5 mg. pyridoxine, 50 mg. calcium pantothenate, and 250 mg. nicotinamide. Crude liver extract (2 cc.) was administered 3 times daily.

The patient showed progressive improvement both by clinical signs and liver function tests (Table 2). The liver size which had been found to be 4 finger-breadths below the right costal margin shortly after entry gradually decreased until no liver edge could be felt at the time of discharge. The elevated icteric index showed a rapid fall. The patient

TABLE 2. LIVER FUNCTION TEST

Date	CBC	A/G Ratio	Cholesterol Esters	Icterus	Bilirubin	Prothrombin	Thymol Turbidity	Ceph. Floc.	2 Hr. Urobilinogen	Galactose Tolerance	Hippuric Acid (Oral)	Bromsulphalein
					(Ind)						(Oral)	
8/25	2.9 50% 11,000	2.8/4.8	175 55%	88	7.4 (.32) chloroform soluble	80%	17	4	1.71 mg.	7 gm./4 hr. urine	4.3 gm. 4 hr. urine	35%
Amniotin begun												
9/14	3.6 72% 9,500	3.2/4.9	255 59%	34	2.1 (.05)		14	3	2.4 mg.	2.5 gm. 4 hr. urine	4.0 gm. 4 hr. urine	
9/25		3.8/3.9		15	1.7 (.06)	75%						
Liver treatment begun												
9/28			180 71%				6	2	1.75 mg.			
10/6	3.5 68% 9,000	4.3/4-1	182 78%	10	1.0 (.04)	70%	5.5	2	.84 mg.			20%
10/15									1.5 mg.			
10/27			188 80%	7	.56(.02)	75%	6	2	1.0 mg.			
11/10	4.0 80% 8,800	4.3/3.0	182 82%	7	.40(.01)	90%	2	2	.5 mg.	.20 gm. 4 hr. urine	5.1 gm. 4 hr. urine	10%

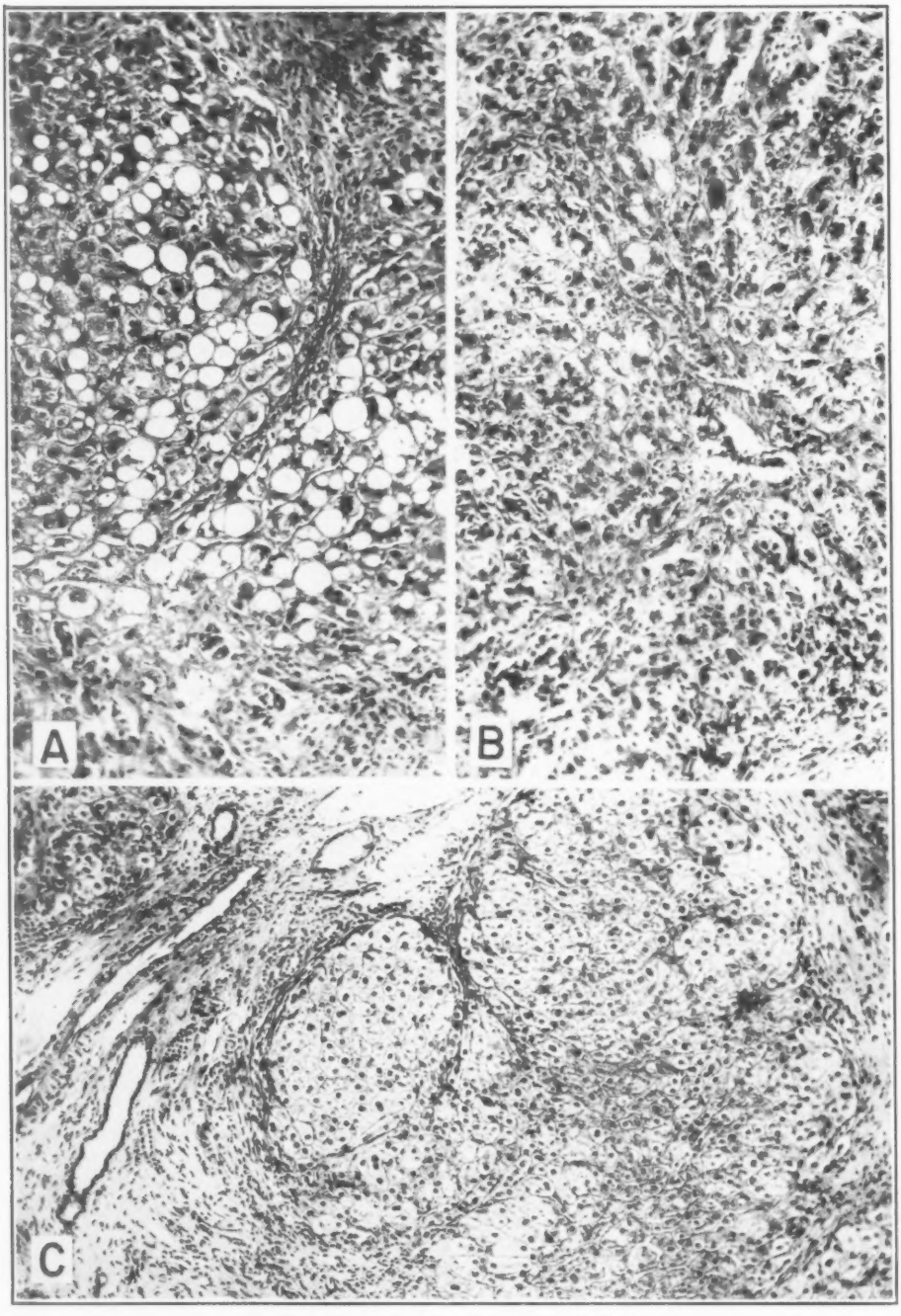

FIG. 1. SERIAL LIVER BIOPSIES

A. Before therapy on August 30, 1948. Marked fatty infiltration. The liver cells show various stages of degeneration. Large quantities of bile pigment are present in canaliculi. Periportal fibrosis is seen with extension of the fibrous septa into the liver lobules.

B. Following estrogen administration on Sept. 30, 1948. Decrease in the degree of fatty infiltration. Fewer degenerating liver cells are seen and the intralobular organization into cords of cells and sinusoids more nearly approaches the normal. Bile pigment is less prominent.

C. After therapy on December 1, 1948. No fatty changes and the liver cells are normal in appearance. An increase in the periportal fibrous tissues with septal extension into the lobule and reduplication of bile ducts is apparent. The lobules are almost completely encircled by fibrous tissue. (Photographs by Wm. L. M. Martinsen, FBPA.)

gained strength, had an increased appetite, and showed a marked decrease in the number of angiomata together with a decrease in the size of the left breast (Table 3). Several weeks after the cessation of estrogen administration, the right breast became swollen and tender. This condition persisted for 2 weeks; then gradually receded.

At the termination of 6 weeks of therapy, the liver biopsy showed marked improvement (Fig. 1), the urinary estrogen excretion had markedly decreased (Table 3), the liver function tests had improved considerably, and the patient was entirely asymptomatic. A marked increase in libido was noted.

TABLE 3. ENDOCRINE STUDIES

		8/29/48	9/28/48	11/22/48
ANGIOMATA				
	Large	38	26	9
	Small	35	21	13
BREAST				
	Right	2 cm. Horiz. x 2 cm. Vert.	2 cm. Horiz. x 2 cm. Vert.	5½ cm. Horiz. x 6 cm. Vert.
	Left	6½ cm. Horiz. x 6½ cm. Vert.	9½ cm. Horiz. x 9 cm. Vert.	5½ cm. Horiz. x 3 cm. Vert.
TESTIS				
	Right	5 cm. long	5 cm. long	6½ cm. long
	Left (atrophic)	2.5 cm. long	2.5 cm. long	2.5 cm. long
ESTROGEN				
	Total*	260 Gamma	85.5 Gamma	60 Gamma
	Free	218 Gamma	75 Gamma	30 Gamma
		Normal values		
PREGNANDIAL†		3.0 mg./24 hrs.		6.6 mg./24 hrs.
KETOSTEROIDS§		3.5 mg./24 hrs.		6.3 mg./24 hrs.

* Normal (male): 7 to 25 Gamma/24 hrs.
† Normal (male): less than 3 mg./24 hrs.
§ Normal (male): 10 to 20 mg./24 hrs.

Discussion. Gynecomastia may be secondary to testicular atrophy[2,17], testicular tumors[6,13], tumors of the adrenal cortex[27], hyperthyroidism[28], pituitary tumors[21], malnutrition[15], vitamin deficency disease[12], recovery from starvation[25], and tumors of renal origin[14]. It may also be induced at varying times by the administration of estrogens, androgens, and desoxycorticosterone.

The mechanism of breast enlargement in association with malnutrition has been attributed by Klatskin *et al.*[15] to either a failure of hepatic inactivation of estrogen or a depression of the pituitary gland from malnutrition with a secondary testicular atrophy and decreased androgen excretion. Their quantitative studies revealed a decrease in ketosteroids, but normal estrogen-androgen ratios with a normal follicle-stimulating hormone titer. In the therapy of gynecomastia secondary to malnutrition, no difference in effect was noted whether a regular, high protein, or high vitamin diet was employed.

The association of gynecomastia and testicular atrophy has been known for some time and this has been attributed by some to the fact that the testes inhibit the growth of the breast in males. Testosterone therapy has been employed on this basis but with conflicting results. Testicular atrophy may be secondary to liver disease according to Marrione[20] who found atrophy in a high percentage of cirrhotics, or may be secondary to malnutrition[22]. Klinefelter

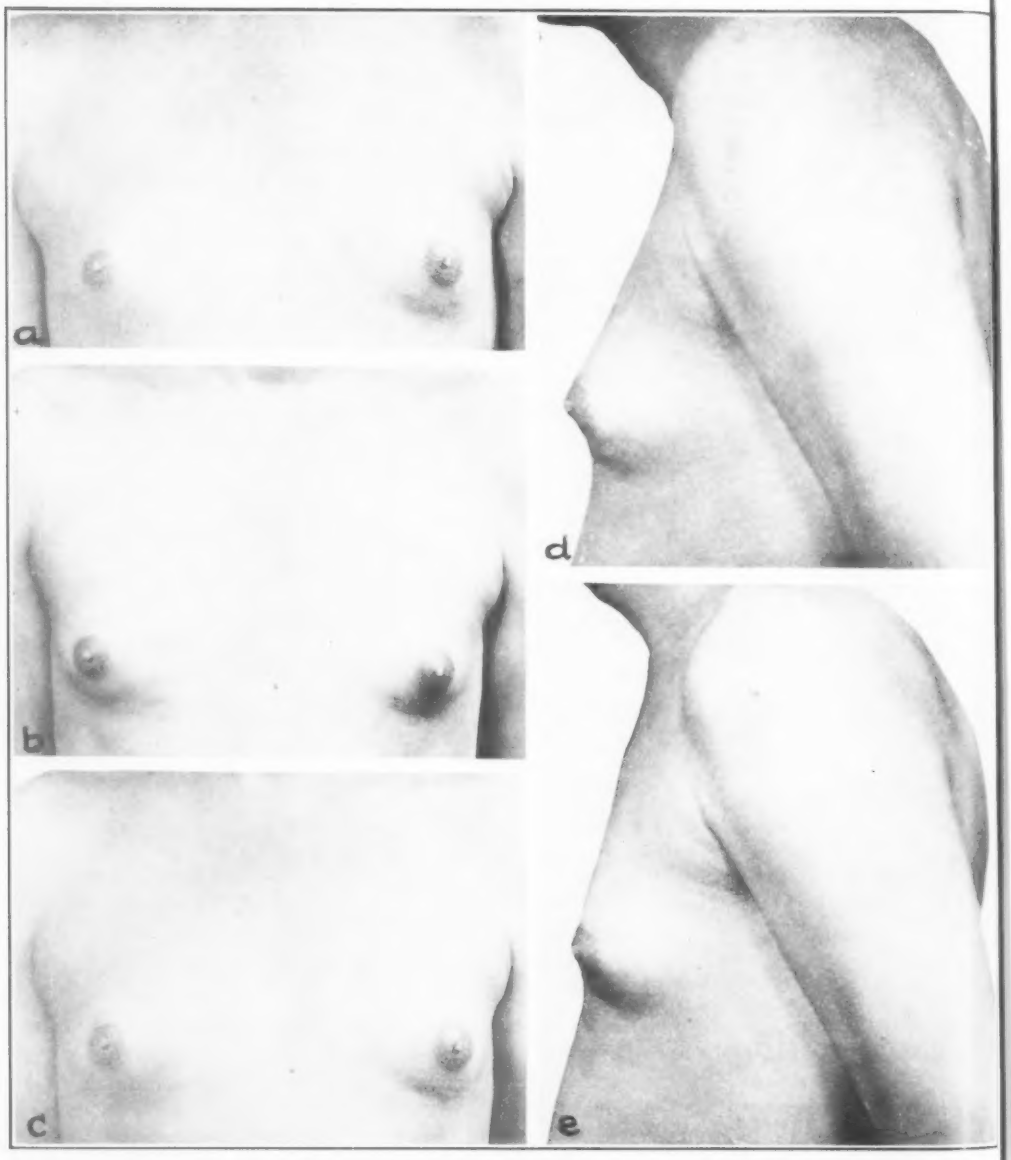

FIG. 2. SERIAL BREAST PHOTOGRAPHS

A. Anterior view of both breasts before therapy, showing enlargement of left breast.
B. Anterior view following estrogen administration, showing enlargement of both breasts as compared to (A).
C. Anterior view showing decrease in size of both breasts (after completion of therapy).
D. Lateral view of left breast before therapy showing marked enlargement.
E. Lateral view of left breast after therapy showing decrease in size. (Photographs by Wm. L. M. Martinsen, FBPA)

et al.[16] have described a syndrome including gynecomastia with atrophic testes showing hyalinization of the seminiferous tubules and postulated that perhaps the inhibiting hormone of the testes on the breast was present in these tubules. Heller and Nelson[11] have described testicular atrophy, azoospermia, and elevation of the gonadotropins frequently associated with enlargement of the breast and loss of hair. They described hyalinization of the seminiferous tubules and clumping of the Leydig cells, and they felt that changes in the Leydig cells might be responsible for the changes in masculine characteristics.

Zondek[30] has stated that the liver is concerned with 95% of estrone inactivation and he has described a test of liver function based on estrogen metabolism. The estrone clearance test is a measure of the ratio of estrone excreted compared to the normal following an intramuscular dose of estrone. He stated that the normal male excreted .5% to 4.5% of the injected estrogen within 48 hours. Patients with hepatitis also excreted a normal percentage unless they were in an advanced state; that is, had lost the function of urea synthesis. Patients with cirrhosis had normal endogenous levels of estrone but excreted an excessive amount following administration. He thought that this test might be useful in determining the prognosis of a given case of liver disease—only in advanced cases with extensive destruction did the liver fail to metabolize estrogens normally.

Glass and associates[7], having also studied this problem, stated that an increased excretion of estrogens had been noted in cases of gynecomastia associated with testicular tumor, adrenal cortical tumor, or following the administration of estrogens. They thought that gynecomastia associated with malnutrition without liver disease may represent a deficiency of the same dietary factor necessary for liver inactivation of estrogens. Glass, Edmondson, and Soll[8] studied the effect of administered estradiol and estrone into men with cirrhosis of the liver and found that injected estrogens lose much of their activity in the presence of normal liver function. They stated that the evidence showed that males with advanced liver cirrhosis excrete urinary estrogens in the free form, and they felt that gynecomastia and testicular atrophy were the result of an excess of circulating free (unconjugated) estrogen. Advanced cirrhosis results in the excretion of a large percentage of estrogen particularly in the free form but all their cases of cirrhosis had some increase in total estrogen excretion. Stealy and Stimmel[29] also pointed out that the conjugation of estrogens given to patients with liver disease was markedly impaired. Other workers[10,24] have likewise shown that 90% of injected estradiol could not be recovered in the urine and postulated that the same mechanism of estrogen metabolism holds for both males and females. They showed that the interconversion of estradiol and estrone could take place, both resulting in estriol (the latter reaction was not reversible).

As for the breast enlargement itself most reported cases have shown[18] hyperplasia of ducts and in increase in periductal tissue—the ducts elongate, become tortuous, develop thickened lining (epithel) and show an infiltration of macrophages in the periductile tissues.

Interpretation of Results: A number of interesting observations can be made after an analysis of this case. Improvement in the liver status was striking on a regular hospital diet before any supplementary therapy was begun, as evidenced by biopsy, decrease in size, and function tests. The

administration of estrogens was apparently not toxic to the damaged liver since improvement occurred during and after the estrogen administration. In addition, the angiomata count decreased while on estrogens; this also indicated liver improvement.

A correlation between the titer of free and total estrogens and the status of liver function was strikingly illustrated in our study. The fall in estrogen excretion and particularly the decrease in the ratio of free to total estrogens paralleled the improvement in liver functions. This correlation was also demonstrated in that the total estrogen excretion was less after estrogen administrations than without estrogens because of the improvement in liver function during this period.

The changes in breast size were also somewhat correlated with estrogen titers but lagged behind the rate of liver improvement. It is difficult to explain the unilateral gynecomastia except by assuming a different degree of sensitivity to circulating estrogens in the two breasts. In explaining the late enlargement of the right breast following estrogen administration we must again assume a difference in local factors in the two breasts. Klatskin has pointed out that in gynecomastia secondary to malnutrition the breast enlargement may occur not during the period of malnutrition but rather during the recovery phase while on a therapeutic regimen.

The increase in urinary keto-steroids, increase in libido, and increase in the size of the right testicle indicates a close correlation between liver function, adrenal function, and gonadal activity. Lloyd and Williams[19] have pointed out that cirrhosis of the liver is frequently associated with a decrease in lipoid content of the adrenals and atrophy of the testes. They also emphasized that the 17-ketosteroid excretion of male patients with cirrhosis is lower than can be explained on the basis of absent gonadal steroids excretion alone – this suggests that adrenal hormone production is less than normal. This may be the result of high estrogen titers in the blood since this is known to inhibit adrenal function. Lloyd and Williams have postulated that the decrease in the inactive oxidative products of estrogen, which occurs when a diseased liver is unable to inactivate estrogens and form these oxidative products, leads to a decrease in formation of adrenotrophin from the pituitary. This in turn leads to decreased adrenal function with loss of axillary hair and a decrease in the urinary 17-ketosteroids.

The decrease in the total number of spider angiomata during estrogen administration is in contradistinction to the findings of Bean[1] who was able to produce "spiders" by the administration of estrogen, and may have been due to the rapid improvement in liver function.

Summary. 1. A review of the relationship between cirrhosis, gynecomastia, and endocrine changes has been given.

2. A detailed metabolic study of a case of cirrhosis with unilateral gynecomastia and other feminizing features has been presented. A careful study of endocrine titers by a modification of previously described methods has been carried out.

3. The correlation between the condition of the liver, the presence of breast changes, and the degree of estrogen inactivation and total excretion has been demonstrated.

4. A striking response in liver function to an ordinary diet, together with a lack of toxic effect on the liver by the administration of estrogens, was noted.

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LIVER FUNCTION IN DIABETES MELLITUS*

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Diabetes mellitus in man is still a syndrome of unknown etiology. The major laboratory indications of the disease, hyperglycemia and glycosuria, may occur in a great variety of experimental conditions and disease states. Hyperglycemia and glycosuria can occur with thyrotoxicosis, Cushing's syndrome, liver disease, pituitary lesions and adrenocorticotrophic hormone administration[1].

In most instances the hyperglycemia can be alleviated by the administration of insulin. This would suggest that an insulin deficiency, either relative or absolute, is the common denominator; but the diabetic state which ensues after total pancreatectomy in man is mild and readily controlled by 25 to 40 units of insulin per day[13]. From an experimental standpoint Soskin has data which point to the liver rather than the pancreas as the major organ in carbohydrate metabolism. Soskin[10] found that the hepatectomized dog had a decreased glucose tolerance, whereas the pancreatectomized animal with a constant insulin infusion had a relatively normal glucose tolerance.

There have been many attempts to incriminate the liver as a factor in the etiology of clinical diabetes, and most of the studies have revealed some impairment in various of the liver function tests. Gray *et al.*[3], using the colloidal gold test, found a positive test in 37% of 241 patients. Moreover, they observed the highest incidence of positive tests in the more severe diabetics, particularly those with a history of diabetic acidosis. Meyer, in 1931[7], concluded that hepatic dysfunction was a frequent occurrence in diabetes mellitus, but the tests used are now recognized as inferior, and many of his patients had complicating biliary tract disease. Rabinowitch[8], who examined 3000 cases from a diabetic clinic, found hyperbilirubinemia in 27.4% when 0.2 mg. per 100 cc. of bilirubin in the blood was taken as the upper limit of normal. Furthermore, he found that a similar percentage of patients had an elevated urine urobilinogen. His upper limit of normal for bilirubin would now be recognized as low, but there is no ready explanation for the elevated urine urobilinogen. Possibly some of these patients had hepatitis, for it is now realized that homologous serum hepatitis is not uncommon in clinics where frequent venipunctures are done.

It should be appreciated that even present day liver function tests are relatively crude and that minor deviations from the normal in any one test should not be interpreted as a manifestation of liver disease. Also, little reliance should be placed upon certain non-specific tests such as the colloidal gold and cephalin flocculation, as these tests are difficult to run in a routine

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clinical laboratory, and slightly positive tests are even more difficult to interpret.

In this study 8 of the commonly accepted liver function tests have been carried out on a series of 25 diabetics in whom there was clinically no other etiological factor for liver disease. In 15 of the patients the studies were made within 48 hours of their admission to the hospital in severe diabetic acidosis. In 3 cases a liver biopsy was done to detect any changes in the histology of the liver. The tests employed were the bromsulfalein retention at 45 minutes, using 5 mg. per Kg., the thymol turbidity[5,6], the cephalin flocculation[4], the van den Bergh 1 minute and 30 minutes[2], the prothrombin content[11], the urine urobilinogen[12], the icterus index and the serum proteins. It was not possible in every patient to do all the tests mentioned, but in every case sufficient tests were done to give a spectrum of liver function.

TABLE 1.--RESULTS OF LIVER FUNCTION TESTS IN 25 DIABETICS

Patient	Duration of Diabetes	Age & Sex	Previous Insulin Dose Day BBG--PZI		BSP % retention at 45 min.	Serum Bil. mg. per 100 cc 1 min.	30 min.	Prothr. Cont. %	Thymol Turb.	Ceph. Floc.	Serum Alb. gm.%	Prot. Glob. gm.%	Urine Urobil. Ehrlich U.	Icterus Index
1. P.D.	15 yrs.	30 M	40	40	0	0	.2	98	.88 (5)	0	3.8	2.5		
2. M.F.	8 yrs.	37 F		50	0			100		1+				5
3. E.G.	4 yrs.	32 F		35	0			85		0				5
4. N.H.	10 yrs.	47 F	20	10	0	0	.02	72	.77	1+				
5. J.M.	1½ yrs.	18 M		20	0	0	.02	100	.3	0				
6. P.M.	1½ yrs.	23 F		12	0			75	.52	0			.6	6
7. W.S.	19 yrs.	55 M	10	40	8	0.2	0.4		.63				.8	
8. J.P.	6 yrs.	28 M		60	0	0.2	0.2		.72		4.1	3.1	.4	
9. C.D.A.	15 yrs.	42 F	45	40	4			75		0			.6	5
10. S.G.	6 yrs.	22 M		60	0	.16	.58	100	.54	1+			.6	
11. E.M.	4 yrs.	35 F	30	30	0			68		1			.4	4
12. J.I.	4 yrs.	25 M		40	2			86		0			.6	5
13. T.D.	5 wks.	33 M	0	0	0	.1	.4	90	.64	0			.5	
14. M.K.	15 yrs.	42 F		40	0	.2	.4	90	.7	1+	4.0	2.1	.2	
15. F.M.	12 yrs.	38 F		35	0	.15	.6	75	.68	1+	3.9	2.0	.5	*
THE ABOVE TESTS WERE DONE WITHIN 24 TO 48 HOURS OF ENTRY TO THE HOSPITAL IN SEVERE ACIDOSIS**														
16. C.L.	6 yrs.	55 M		60	1			100	3. (6)		5.4	1.8	.6	5 *
17. P.E.L.	9 yrs.	52 M			2	0.8	1.4	80	2.5		5.6	2.0	0.8	
18. H.H.	1st Dg.	56 M		20	8	0.4	1.2	50	4.		6.2	1.6		5
19. C.V.T.	3 mos.	60 M			1			75	2.		4.4	2.6		5
20. N.B.	7 yrs.	55 M			4	0.2	1.0	100	5.					
21. J.N.	1 yr.	35 M	20	60	0	0.2	0.8	92	5.		5.2	3.6		*
22. J.A.	1 yr.	61 M		45	0	0.1	0.4	50	2.5		4.6	2.8	1.2	
23. A.W.	12 yrs.	51 M		70	15	0.2	0.4	100	4.		4.0	3.0	0.48	
24. H.H.	6 mos.	50 M			5	0.4	1.2	75	5.		4.8	1.1		
25. J.H.	3 yrs.	55 M		10	2	0.3	0.7	85	1.		4.2	2.8		

* Biopsy with normal liver.

** All of the patients in acidosis had a CO_2 combining power of less than 20 volumes %.

Results. Although this series is small, the results (see Table 1) indicate that there is little if any derangement of liver function in diabetes as measured by the usual liver function tests. In the 15 patients who entered the hospital in acidosis, in whom one might expect a maximum derangement of carbohydrate metabolism, and by that token perhaps of liver function, the liver functions were strikingly normal. In only 1 patient of the acidosis group was there any significant bromsulfalein retention, and this was only 8%, which is very close to the upper limits of normal. Another case showed 15% retention, but this patient had some congestive failure. In no case of the series was there a complete battery of tests indicating hepatic disease.

In 3 of the patients whose livers were somewhat enlarged on physical examination, the histological sections on punch biopsy were perfectly normal. Even special strains for glycogen and fat revealed no abnormality.

It is appreciated that the function of the liver concerned with carbohydrate

metabolism may not be measured by any of the tests employed and that some new test may reveal an abnormality of liver function. The galactose tolerance test which is a good test of liver function, might be expected to be abnormal in the diabetic with his deranged carbohydrate metabolism, but the results were found to be no different in a series of 10 normals and 10 diabetics reported by Roe and Schwartzman[9].

This study furnishes no evidence that hepatic disease is associated with diabetes mellitus. This is in agreement with Wilder[14] who found evidence of hepatic disease in only 0.7% of 2584 cases of diabetes mellitus, and only rarely did there seem to be any causal relation between the 2 diseases.

Summary. A battery of the usual liver function tests has been employed in the study of a series of 25 diabetics, in 15 of whom there had been a recent episode of acidosis. No evidence was obtained to indicate that impaired liver function is associated with clinical diabetes mellitus.

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THE INFLUENCE OF PHYSICAL THERAPY PROCEDURES ON THE INTRA-ARTICULAR TEMPERATURE OF NORMAL AND ARTHRITIC SUBJECTS*

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Although physical therapy has long been regarded as one of the therapeutic agents of proven value in arthritis, we know of no studies to determine changes in the temperature of the diseased joint following the use of these various procedures. Knowledge of the best way to produce these changes is obviously of immediate and considerable practical value. Lonergan[3] found a 1° F. rise in the temperature of a dog joint on the application of long wave diathermy for a period of 1 hour. Continuous application of this agent resulting in the death of the animal from shock produced a rise of 7° F. in the left hip joint. Lonergan also reported one experiment in which long wave diathermy was applied to the human knee joint. A thermocouple was placed in the popliteal space with the knee acutely flexed on it. After a 70 minute treatment, a temperature rise of slightly more than 4° F. was observed. Several other reports[2,4] have appeared on the joint temperature of dogs following heating. One group of investigators[2] has calculated cooling curves, and estimated relative rates of circulation through the joint tissue. Horvath and Hollander[1] have determined the temperatures of knee and elbow joints in both normal subjects and patients suffering from joint diseases. An excellent correlation between the joint temperature and the clinical activity in patients suffering from rheumatoid arthritis was observed.

Methods. The procedures employed to modify the joint temperature will be given at appropriate places in the text. Only a single agent was employed on a patient at any one time. The skin and deep temperatures were measured by methods previously described[1]. The subjects were supine and the thermocouple was in place within the joint for at least 20 to 30 minutes prior to the control observations. In the majority of the tests environmental temperature was 24° ± 2° C.; in the remaining it was 18° C.

Results. Passive motion of the joint through its pain-free range is a common therapeutic procedure. The data presented in Table 1 were obtained prior to, and following, such movement in 8 subjects. Although skin temperature over the joint was not influenced by this procedure, a mean elevation of 0.8° F. occurred within the joint. However, considerable variation in response was observed. In Subject 6, only the first few movements were accomplished without pain, and, since the range was definitely limited, it was impossible to move the joint to any great extent. The

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TABLE 1. THE INFLUENCE OF PASSIVE MOVEMENT° OF THE KNEE JOINT ON THE TEMPERATURE WITHIN THE JOINT

Patient	Initial Temperature °F.	Maximum Change °F.
1. Normal	90.6	0.5
2. Normal	88.6	2.1
3. Rh. Arthritis	96.0	2.0
	96.6	0.1
4. Rh. Arthritis	90.8	1.4
5. Rh. Arthritis	92.8	−0.2
6. Rh. Arthritis	92.3	−0.9°°
7. Degen. Joint Disease	93.9	1.4
8. Gout	96.1	0.8
Mean Change		0.8

° 10 to 15 movements without pain.
°° Painful.

the sixth subject the elbow was treated and the maximum elevation in this joint was 3.6° F. while the skin temperature rose 1.6° F. A significantly greater rise ($t = 1.88$) in the joint than in the surface temperature was observed. The mean difference between the 2 positions was 1.6° F. This variation was more apparent when higher energy inputs were being employed. A typical cooling curve following this type of heat therapy is shown in Figure 1. The sharp initial drop and succeeding retarded rate of cooling was observed in all patients.

Table 3 contains the data obtained

TABLE 2. EFFECT OF MICROWAVE° ENERGY (12.2 cm.) ON THE TEMPERATURE OF THE KNEE JOINT

Patient	Initial Temperature °F. Surface	Initial Temperature °F. Joint	Maximum Increase °F. Surface	Maximum Increase °F. Joint
9. Reiter's Syn.	86.0	90.6	6.0	5.7
Reiter's Syn.	87.5	89.4	6.4	8.4
10. Rh. Arthritis	91.9	92.9	5.0	8.2
11. Rh. Arthritis	84.5	88.1	6.3	6.9
13. Rh. Arthritis	88.9	92.9	7.6	3.6
14. Rh. Arthritis	93.7	94.8	2.4	2.5
Rh. Arthritis	94.0	96.0	1.1	1.1

° All applications were for a period of 15 minutes. Patients 9 to 12 were given 50 watts; patients 13 to 14 were given 35 watts.

degree and intensity of movement probably modify the rise in temperature. Active weight bearing movements were also performed in 2 normal subjects and a mean rise of 2.3° F. was observed. More information on this aspect will be presented when the amount of work performed by the patient's joint can be accurately evaluated.

Heating of the joint and adjacent tissues by the application of high frequency electrical energy was studied in a number of subjects. A micro wave generator (wave length 12.2 cm.), employing a director 4 inches in diameter, placed at a distance of 2 inches from the joint was used. The duration of the heating period was exactly 15 minutes. The data obtained in 5 patients are presented in Table 2. In following the application of conventional short wave diathermy. The inductive method with 3 turns of the coil around the joint was employed. The heating period was 20 minutes. The maximum elevation of the joint temperature was approximately to a level of 101° F. The initial joint temperature apparently exerted no influence upon this final value. Note especially the changes in Subject 15, a normal individual, and in Subject 18, an individual suffering from degenerative joint disease. The elevation of both joint and surface temperatures was approximately equivalent, the mean surface temperature being some 0.6° F. higher than the mean joint temperature. In Figure 2 are shown typical cooling curves obtained on a normal individual and on an individual suffering from

rheumatoid arthritis. The differences between the two cooling curves are mainly those relating to the duration and rate of cooling of the joint following therapy. The relative rates of cooling were quite different in different disease entities. Calculations of K, the cooling constant, on 4 types of individuals are presented below. In the normal subject K was −1.14; in quiescent rheumatoid arthritis, −0.90; active rheumatoid arthritis, −0.56; and for degenerative joint disease, −0.35.

The application of an infra-red baker to the knee and surrounding areas for a period of 20 minutes resulted in rather large increases in surface temperature with minimal elevations of the

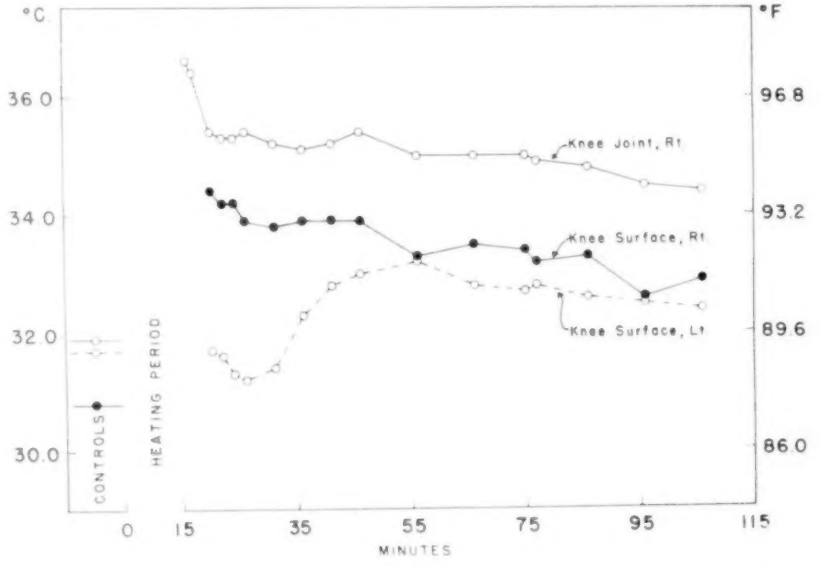

FIG. 1. The joint and surface temperatures in a patient with Reiter's disease before and after the application of micro wave energy with a 4 inch circular director and a power output of 50 watts.

TABLE 3. ELEVATION OF THE TEMPERATURE OF THE KNEE JOINTS AND SURFACES FOLLOWING VARIOUS THERAPEUTIC PROCEDURES

Patient	Mode and Duration of Treatment	Initial Temperature °F. Surface	Initial Temperature °F. Joint	Maximum Temperature °F. Surface	Maximum Temperature °F. Joint
15. Normal		85.2	90.8	9.6	10.2
16. Rh. Arthritis	Short Wave	84.7	86.0	12.9	9.8
17. Rh. Arthritis	Diathermy	91.8	96.6	3.6	4.6
18. Degen. Joint Disease	(20 minutes)	92.8	96.4	5.4	4.8
19. Reiter's Syndrome		89.8	93.3	6.7	5.7
19. Gout		—	96.0	—	3.7
20. Rh. Arthritis	Infra Red Baker	91.0	92.8	8.2	1.7
21. Degen. Joint Disease	(30 minutes)	92.1	90.6	5.9	4.4
22. Rh. Arthritis	Luminous Lamp (20 minutes)	94.8	97.3	5.7	1.0
23. Rh. Arthritis	Paraffin Pack	96.1	97.0	6.6	0.8
24. Rh. Arthritis	(26 minutes)	89.9	95.2	15.6	3.1

° Paraffin temperature 148°F.
°° Paraffin temperature 130°F.

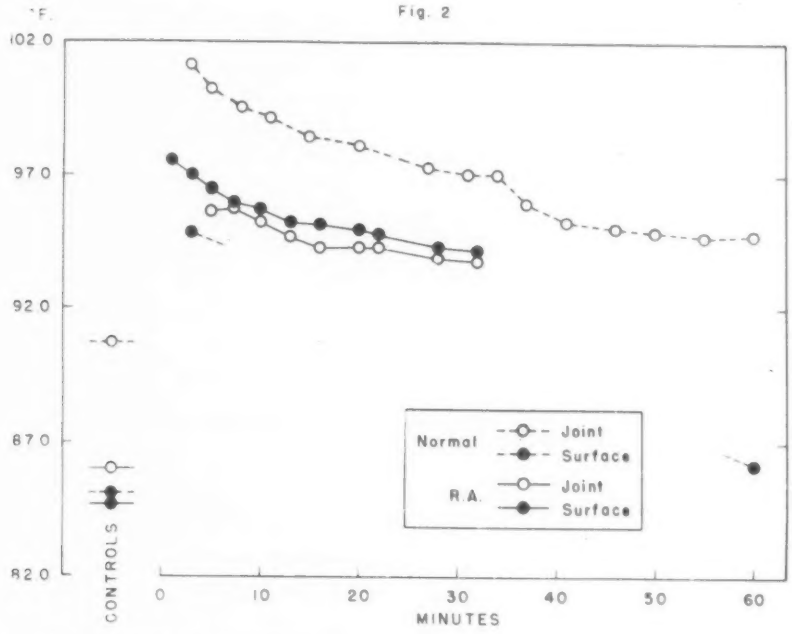

FIG. 2. The joint and surface temperatures in a patient with quiescent rheumatoid arthritis and a normal subject before and after local heating for 20 minutes employing short wave diathermy (induction coil method).

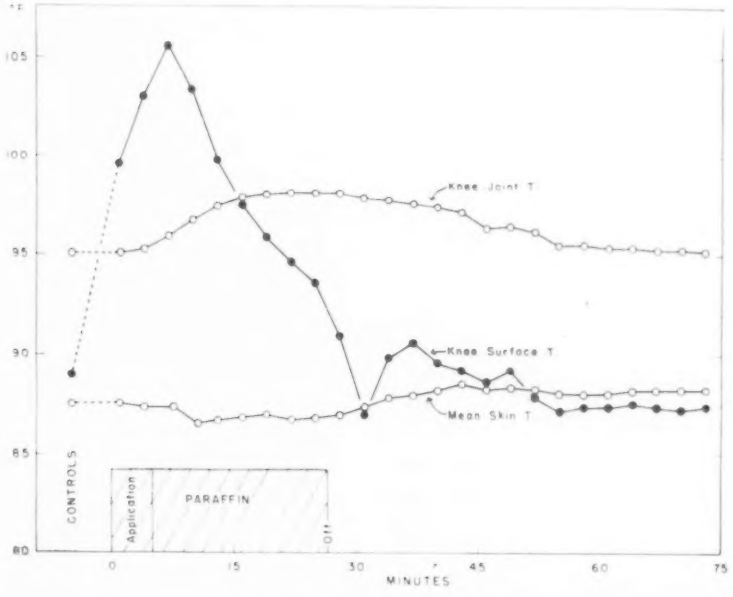

FIG. 3. The joint temperature in a patient with rheumatoid arthritis before, during, and after application of paraffin.

deep or joint temperature. The mean maximum change in joint temperature was +3.3° F. When an infra-red lamp was applied for a period of 20 minutes a small change, 1° F., occurred in the deep temperature, whereas the surface temperature rose approximately 6° F. at the completion of the treatment.

The effectiveness of the application of paraffin over a joint depends to a great extent upon the temperature at which the paraffin is being applied. In one experiment in which the temperature of the paraffin was 130° F. a mean elevation of the joint temperature to 3.1° F. was observed. In Figure 3 is shown the maintained response of the joint temperature to this therapeutic procedure. If, however, the paraffin was too hot, namely at a temperature of 148° F., there was little elevation in the joint temperature. The discrepancy between these procedures probably lies in the fact that the thickness of the layers is definitely related to the temperature of the paraffin being applied.

Several experiments were performed in which individuals were subjected to hydrotherapeutic procedures. Treatment in the Hubbard Tank with the water temperature 101° F. resulted in an increase in joint temperature of 0.7° F. It should be noted that the rectal temperature during this period of immersion had also risen 0.6° F. This effect was relatively transitory and disappeared within 20 to 30 minutes. In additional experiments it was attempted to determine the influence of reflex vaso-dilation on the joint temperature in the extremity being reflexly vaso-dilated. The knee joint temperature of the leg that was immersed up to the knee failed to rise as a consequence of the treatment. This was interesting, in view of the fact that conduction heat was apparently of no great importance in raising the joint temperature. The ankle joint on the contralateral limb had its temperature measured during the same interval and failed to exhibit any change during and following treatment. On the other hand it should be noted that there was a definite reflex vaso-dilation as evidenced by the rise in the toe temperature of the contralateral side. The toe temperature was elevated 9° F. to a final temperature of 94.6° F. It is significant that reflex vaso-dilation of the skin vessels was not accompanied by a similar reflex vaso-dilation in the deep vessels.

Discussion. Classification of heating procedures by their effect on joint temperature is now possible. This method of determining temperatures may also prove to be a means of measuring the efficiency of circulation in the synovial membrane. The various procedures employed to elevate the intra-articular temperature do so in a manner dependent apparently upon their relative ability to penetrate to the deeper tissues. This is most evident in comparison of the results of infra-red irradiation, where a mean rise in temperature of slightly over 3° F. was observed, with values of 6° to 8° F. elevation of temperature following the application of conversive types of heating. It is also interesting to note that the duration of the cooling curve appears to be primarily a reflection of the intensity of the elevation of the joint temperature.

The significance of the various types of cooling curves observed in individuals suffering from joint disease is not at the moment apparent. It is interesting, however, that the cooling curve is more prolonged in those individuals suffering from degenerative joint disease. A probable explanation of this observation lies in 2 factors: 1, the excessive amount of fibrous tissue in the thickened synovial membrane and increased adipose tissue around the joint which interferes with ready loss of heat from the part; 2, definite changes in circulation within the diseased joint. It

is extremely suggestive that the cooling curve of normal individuals is so much more rapid than that of those suffering from arthritic involvements.

It has not yet been shown that raising the joint temperature, in treating various forms of arthritis, is necessarily beneficial. It is well known that in many cases of active arthritis those forms of physical therapy that raise the temperature most, namely short wave diathermy and micro wave, clinically appear to aggravate pain in the joints. On the other hand forms of therapy like infra-red which have minor effects on the joints and exert their primary effects on the surface appear to be of much greater value. It is apparent from these results that re-evaluation of the procedures of physical therapy chosen for treatment in arthritic disorders should be made with the reaction of the joint tissues in mind and should not be dependent purely upon surface changes. This is of greater interest since it has been shown[1] that the changes in joint circulation do not necessarily parallel those of the skin but frequently are even opposed, which indicates at least a reflex reciprocal flow of blood between the integument and deeper tissues.

Conclusions. It has been possible to evaluate the results of various methods of applying physical therapy by simultaneous determination of internal joint temperature and surface temperature.

Passive motion of a joint increased joint temperature to a slight degree. A more marked effect was observed following active weight bearing motions.

Passive heating of joints was accomplished by means of short wave diathermy, a micro wave generator, an infra red baker, application of paraffin or immersion in hot water. All these methods of applying heat increased the skin temperature as anticipated.

Following hydrotherapy, however, the joint temperature was only slightly elevated.

More marked heating of the joint was obtained from radiant heat and the application of paraffin to the surface.

The greatest elevation of joint temperature occurred following application of high frequency electrical energy, *i.e.*, short wave diathermy or micro wave. The relative rate of cooling of joints after passive heating was more rapid in normal than in rheumatoid arthritic or osteoarthritic joints.

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THE METABOLISM OF THIOCYANATE AFTER PROLONGED ADMINISTRATION IN MAN*

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Investigations of the distribution of thiocyanate ion in measuring the extracellular fluid volume has resulted in a better understanding of its metabolism during short sojourns within the body[1,5,6,13]. Whereas almost all thiocyanate can be recovered in the urine after a single dose[13], discrepancies between the daily intake and urinary output have been demonstrated after repeated administration of the drug for prolonged periods[1,6,11,12]. In explanation of this, routes of excretion other than the kidneys in man[12], and intra-cellular storage in dogs[1,6] have been suggested, but never conclusively demonstrated. Since thiocyanates are still used in the treatment of essential hypertension and in the estimation of extracellular fluid volume it seemed of importance to determine the fate of this drug after long continued use in man.

Materials. Fifteen cases, 9 normotensive and 6 hypertensive, were selected for study because they had little evidence of impaired renal function or abnormal hydration. They were divided into 3 groups:

Group 1 consisted of 2 normal subjects (the authors) both of whom received single doses of 1500 mg. of sodium thiocyanate§ intravenously. Then, after an interval of 4 weeks, Subject E.D.F. received a single oral dose of 1260 mg. of potassium thiocyanate†. Group 2 consisted of 9 cases hospitalized 7 to 13 days for conditions other than acute illness. Eight received oral potassium thiocyanate in doses to 200 to 400 mg. per day, while 1 received daily doses of 400 mg. of sodium thiocyanate intravenously. In both groups 24-hour, as well as other appropriate collections of urine were made throughout the period of study. Group 3 consisted of 5 cases studied as out-patients at 7 to 14 day intervals for 4 to 15 weeks. Four were selected because of their cooperation and reliability in obtaining 24 hour collections of urine and taking prescribed doses of oral potassium thiocyanate (120 to 360 mg. per day) depending upon the individual case. To avoid criticism of data obtained in this manner, one of us, F.C.M. followed a similar regimen for 4 weeks collecting all urine voided throughout the entire period until no further thiocyanate appeared therein.

Methods. Determinations of the serum concentration of thiocyanate were made by the method of Crandall and Anderson[5], modified[6], and adapted to the Coleman junior spectrophotometer[17]. The "natural thiocyanate color" of the serum[3], which remained constant in any given case from day to day, was determined prior to administration of the drug. From this value (range 0.7 to 1.2 mg. per 100 cc.) correction was made in each instance to obtain the actual serum con-

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§ Sodium thiocyanate in sterile saline containing 50 mg. per cc. used exclusively throughout this study for intravenous administration.

† Potassium thiocyanate "Enseals"—Eli Lilly Co., Indianapolis, Indiana, was used exclusively throughout this study for oral administration.

centration of thiocyanate. Urinary thiocyanate determinations were made by pipetting 2 cc. of urine with 10 cc. of 10% trichloroacetic acid and filtering after gentle agitation. Three cc. of the filtrate were then pipetted into each of 2 colorimeter tubes. To one, 3 cc. of ferric nitrate reagent[6] was added and to the other, which served as a blank, 3 cc. of distilled water. Readings were made within 5 minutes with the Coleman junior spectrophotometer at a wave length of 480 millimicrons. A thiocyanate-like color developed by ferric nitrate found in the urine[6] of all subjects while receiving no thiocyanate was determined prior to administration of the drug and correlated with the specific gravity. A factor was thus determined for every 0.001 of specific gravity in each subject and corrections made to determine the actual amount of thiocyanate in each 24 hour collection. The stool specimens were first thoroughly mixed in a Waring blender with known volumes of water and filtered prior to determination of thiocyanate concentration. Blanks were utilized in the same manner as described for the urine, and, because no natural color appeared in the feces, further correction was unnecessary. The thiocyanate content of the sweat (induced by heat) was determined in the same manner as the plasma.

As applied in this study, the term "thiocyanate space" reflects the total fluid volume in which thiocyanate is distributed including the plasma volume and that amount known to enter certain cells[5,13]. Since the fluid volume in this space remains constant under normal conditions of hydration[13,14], repeated doses of thiocyanate should increase the concentration in this fluid volume proportionately, unless after prolonged administration, (1) thiocyanate enters cells to a greater degree, (2) is excreted by routes other than the kidneys, or (3) is destroyed. Because the serum thiocyanate is in relative equilibrium with all components of the "thiocyanate space," the serum increment each day should be equivalent to the increment within the entire "thiocyanate space" throughout any period during administration of the drug. Thus, it should be possible to determine the amount in mg. retained at any moment by multiplying the plasma concentration of thiocyanate in mg. per cc. by the "thiocyanate space" in cc. Furthermore, the per cent daily increment retained within the fluid volume of the "thiocyanate space" as calculated above plus the per cent excreted in the 24 hour urine, feces, and sweat, should approach all of the daily intake, unless, as previously suggested, undue cellular deposition or destruction occurred.

Results. GROUP 1. The subjects of this group were each given a single dose of thiocyanate in an attempt to determine whether all of the drug could be recovered in the urine following acute administration (Table 1). Subject E.D.F., who received 1500 mg. of sodium thiocyanate intravenously excreted a total of 1460 mg., (97%) of the original amount in the urine throughout a period of 14 days. After that time no further thiocyanate could be recovered in the serum or urine. Similarly, Subject F.C.M., who received the same amount of drug intravenously, excreted a total of 836 mg. of thiocyanate during the first 5 days when the experiment was terminated. Multiplying the serum concentration (0.043 mg. per cc.) by the thiocyanate space (15,200 cc.) it was calculated that 654 mg. of the drug remained within the fluid volume of the "thiocyanate space" after 5 days. Therefore, a total of 1490 mg. (836 + 654 mg.), or 98.7%, of the dose could be accounted for at that time (Table 1). At another time, subject E.D.F. received 1260 mg. of oral potassium thiocyanate as a single dose. Following administration of the drug all urine voided was collected until thiocyanate failed to appear therein. After 13 days, 1212 mg. of the original 1260 mg. (96%) of drug administered was recovered. Obviously, therefore, almost all thiocyanate was accounted for by urinary excretion after single doses of the drug whether administered by the intravenous or oral route.

It is of interest that whereas in dogs receiving intravenous thiocyanate a marked increase of the apparent volume of distribution occurred with time[6], the apparent volume of distribution after single intravenous doses in both subjects of Group 1 of the present experiments in man increased only slightly throughout the first 48 to 72 hours, thereafter returning towards

TABLE 1.—ACUTE ADMINISTRATION OF THIOCYANATE PER CENT OF DRUG RECOVERED AFTER SINGLE DOSE

Subject	*Route and Amount Thiocyanate Given Mg.*	*Time From Administration Days*	*Thiocyanate Space cc.*	*Serum Conc. Mg. %*	*Amount of SCN to be Accounted for Mg.*	*Total Urinary Output Mg.*	*Total Urinary Recovery of SCN Per Cent*
E.D.F.	1500 I.V.	14	15,300	0	1500	1460	97.3
F.C.M.	1500 I.V.	5	15,200	4.3	846	836	98.7
E.D.F.	1260 Oral	13	15,300	0	1260	1212	96.2

TABLE 2.—THE APPARENT VOLUME OF DISTRIBUTION OF SODIUM THIOCYANATE DURING 5 DAYS AFTER SINGLE INTRAVENOUS INJECTION

					Sodium Thiocyanate				
Subject	*Age*	*Sex*	*Weight Kgm.*	*Time After Injection Hours*	*Dose Intravenous Mg.*	*Serum Concentration Mg. %*	*Output Urine Mg.*	*Amount Retained Mg.*	*Volume of Distribution* — *Liters*	*Volume of Distribution* — *% Body Weight*
				2	1500	9.8	13	1487	15.2	21.4
				4		9.3	26	1461	15.7	22.1
				6		9.1	35	1426	15.7	22.1
F.C.M.	35	M	71	24		7.1	230	1196	16.9	23.8
				48		6.4	244	952	14.9	21.0
				72		5.7	110	842	14.8	20.9
				96		4.9	99	743	15.2	21.2
				120		4.3	70	673	15.6	22.5
				2	1500	9.7	23	1477	15.3	21.0
				5		9.3	22	1455	15.7	21.5
				7		9.0	14	1441	16.0	21.9
F.D.F.	36	M	73	24		7.2	233	1208	16.8	23.0
				48		5.5	237	971	17.6	24.1
				72		4.6	194	777	16.9	23.1
				96		—	151	626	—	—
				120		3.2	115	511	16.0	21.9

the values obtained at the end of 2 hours which averaged 21.2% of the body weight (Table 2). Although these values are higher than those obtained with inulin[10], they correspond to those of other workers[10,13] for the apparent volume of distribution of thiocyanate in man.

GROUP 2. In all of these cases receiving continued daily doses of the drug the serum concentrations of thiocyanate increased rapidly throughout the first 4 to 5 days, and then remained relatively constant. (Fig. 1). However, once a serum concentration became established there were wide fluctuations in the total urinary output of thiocyanate from day to day (Fig. 1). That these fluctuations were not due to the dose or serum concentration of the drug was evidenced by the fact that in 2 cases (W.W. and L. W-H.) similar fluctuations were observed not only at the serum levels established after receiving 200 mg. of thiocyanate for 6 days, but also at higher serum levels established after the dose had been increased to 400 mg. per day for several days. Furthermore, in all cases the sum of the per cent retained in the "thiocyanate space" and the per cent excreted in the urine approached 100% of the daily intake only during the first 2 to 3 days. Thereafter, an average of 74% (range −78 to +195% of the daily intake could be accounted for (Fig. 1).

In 3 cases 24 hour stool collections

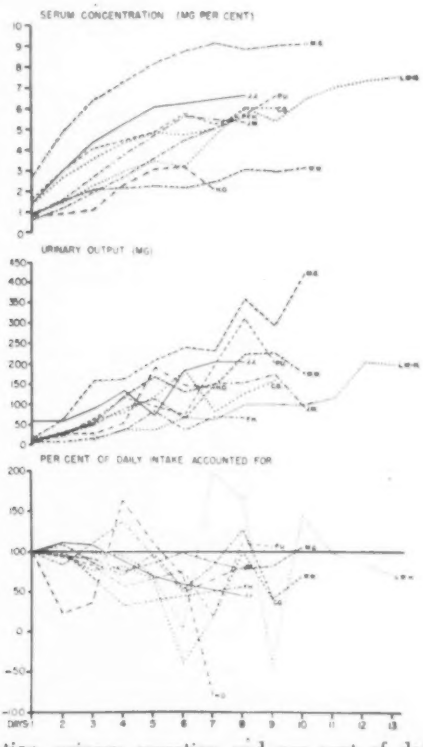

FIG. 1. Serum concentration, urinary excretion and per cent of daily intake of thiocyanate accounted for in the subjects of Group 2. The urinary output fluctuates widely after the first 4 to 5 days and after the first 2 to 3 days less than 100% of the daily intake is accounted for in the majority of instances. Subjects L. W-H. and W. W. received 200 mg. of oral potassium thiocyanate a day for 6 days, then 400 mg. for the remainder of the period of study.

made on 3 to 6 different days at different serum concentrations revealed an average daily thiocyanate excretion in the feces of 3.7 mg. (range 1 to 20 mg.) which represented a negligible portion of the intake. Moreover, in 1 case (F.C.M.) with a serum concentration of 4.9 mg. per 100 cc. the concentration in the sweat (heat induced) was only 0.8 mg. %.

GROUP 3. All cases received oral potassium thiocyanate for 2 to 15 weeks in amounts sufficient to maintain blood levels from 4 to 14 mg. per 100 cc. for periods of 2 to 8 weeks. Throughout the period when blood levels were relatively constant, weekly determinations of the 24 hour urinary output in all cases revealed discrepancies between the daily intake and the total urinary output similar to those noted in Group 2.

In 4 cases after varying periods of daily administration thiocyanate was discontinued and all urine collected, either to the point of complete disappearance of thiocyanate from both the serum and urine, or to a point of known serum concentration. In these cases the amount of thiocyanate recovered in the urine, in contrast to the results obtained when a single dose was given, ranged from 20 to 36% less than the amount calculated to have remained in the fluid volume of the "thiocyanate space" at the time of withdrawal (Table 3).

In order to confirm the above results, one of us, F.C.M., ingested 4440 mg. of potassium thiocyanate in divided doses of 360 mg. per day for a period of 13.3 days. All urine was collected throughout this period and continued after the drug was withdrawn until the serum and urine were completely cleared of thiocyanate. The average values of 3.7 mg. per day for loss in the feces and 8 mg. per day (0.008 mg. per cc. x 1000 cc.) for loss through imperceptible sweat[15] were used to calculate the total loss via these routes. Calculated thus, the fecal and imperceptible sweat loss was 269 mg. throughout the 23 day period, while the urinary recovery was 2670 mg. The total recovery of 2939 mg. (2670 mg. +269 mg.) of the administered 4440 mg. left a deficit of 34% of the thiocyanate administered. In contrast, after acute administration in the same subject there was a deficit

TABLE 3. PROLONGED ADMINISTRATION OF THIOCYANATE PER CENT OF DRUG UNACCOUNTED FOR AFTER WITHDRAWAL

At Time of Withdrawal of KSCN

Subject	*Duration of Administration Weeks*	*Serum Concentration Mg. %*	*Calculated Amount KSCN Present in "Thiocyanate Space" Mg.*
K. M.	11	4.5	665
G. B.	15	13.8	1900
M. S.	9	7.1	792
D. M.	4	5.8	1190

After Withdrawal of KSCN

Subject	*Time After Withdrawal Days*	*Serum Concentration Mg. %*	*Total Urinary Output of KSCN Mg.*	*% KSCN Unaccounted For*
K. M.	12	0	483	20
G. B.	28	0	1212	36
M. S.	10	1.6	637	20
D. M.	23	0	939	22

of only 1.3% exclusive of possible excretion via the sweat or feces.

Discussion. The results of these studies indicated that temporary cellular storage occurred after the acute administration of thiocyanate since the "apparent volume of distribution" increased during the first 48 to 72 hours. However, such storage was only transient and almost all of the drug was recovered in the urine.

In contrast, during prolonged administration there were marked discrepancies between the daily intake and urinary output, confirming the observations of previous authors[1,6,11,12]. Such discrepancies apparently occurred coincident to the establishment of a relatively stable serum concentration regardless of the daily dose or of the route of administration. That routes of excretion other than the kidneys did not explain such discrepancies during prolonged dosage was indicated by the fact that negligible amounts of the daily intake were recovered in the stool and sweat despite relatively high serum concentrations.

Since thiocyanate was not excreted in the feces or sweat to any significant degree, the failure to account for all of the drug administered after prolonged use suggested that it had either entered cells or had been altered within the body. If intracellular storage had occurred the subjects who had received thiocyanate for long periods (Group 3) would have accumulated considerable amounts during the 2 to 15 weeks of administration. After such cellular accumulation withdrawal of the drug should have been followed by an even greater urinary recovery of thiocyanate than had been calculated to remain within the "thiocyanate space." However, upon withdrawal of the drug after prolonged administration no evidence of such intracellular accumulation was apparent in the urinary recoveries. In fact, the total urinary excretion was even less than that calculated to have been in the "thiocyanate space" at the time the drug was discontinued. This indirect evidence was confirmed by the results of Subject F.C.M. In this instance, whereas after the acute administration of a single dose only 1.3% of the total amount given was not recovered, after prolonged administration 34% of the amount ingested was lost. Since excretion by routes other than the kidneys and intracellular storage failed to explain such great losses of thiocyanate it was concluded that permanent alteration of the ion must have occurred within the body after prolonged dosage.

The recent studies of Wood and Williams[16] using radioactive thiocyanate demonstrated destruction of minute amounts of the ion in the thyroid of rats after 24 hours. It is possible in view of the present investigation that greater amounts of the thiocyanate ion would have been destroyed after long continued administration. Although the product formed in the thyroid gland has not been determined, these same authors had previously demonstrated that in rats minute amounts of thiocyanate may be converted into sulfate[19]. Furthermore, Estes and Keith[7] recently reported elevation of the serum sulfate in a few patients who had received thiocyanate for long periods of time. Although suggestive, these studies do not prove that thiocyanate is catabolized to sulfate in man; nor do they exclude the possibility that thiocyanate is utilized to form other sulfur containing products within the body.

It is impossible to determine from the present data whether the clinical effects of thiocyanate in hypertensive patients are associated with this apparent mechanism for destroying thiocyanate after prolonged administration. That such a relationship may exist, however, is suggested by the

observations that the thiocyanate ion does not exhibit hypotensive properties upon acute administration in doses sufficient to obtain therapeutic blood levels[9], while clinical responses to the drug, when they occur, frequently are not observed until after several weeks of continued administration[2,4].

Summary and Conclusions. 1. After a single dose of thiocyanate nearly all of the drug can be accounted for on the basis of urinary excretion.

2. By contrast, after prolonged administration either orally or intravenously, discrepancies occur between the total amount excreted and the amount retained, suggesting that under these circumstances the drug is either stored intracellularly or destroyed *in vivo*.

3. Following withdrawal of the drug after a period of prolonged dosage the total amount recovered in the urine is far less than that calculated to be present at the time medication was discontinued, indicating that during prolonged administration destruction rather than storage of thiocyanate ion occurs.

4. Negligible amounts of thiocyanate are excreted in the feces or the sweat.

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DIAZOMETHANE POISONING: REPORT OF A FATAL CASE WITH AUTOPSY

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(From the Medical Service of the Jewish Hospital)

The present report is concerned with what is believed to be the first instance of fatal diazomethane poisoning in man. Diazomethane was discovered by Pechmann[9] in 1894. A search of all reference sources available since that year, including all issues of the Quarterly Cumulative Index Medicus and its predecessors, the Index Catalogue of the Library of the Surgeon-General's Office of the United States Army, and various texts and monographs on toxicology, chemistry and industrial medicine too numerous to mention, reveals but a single published clinical case of diazomethane poisoning. This was reported by Sunderman, Connor and Fields[10] in 1938. The lack of emphasis on the extreme toxicity of this agent in the chemical literature, which was noted by these authors, apparently persists at the present writing.

Pechmann[9] described diazomethane as being extremely poisonous. Various ill effects experienced by those working with the gas were subsequently noted briefly. These included denudation of the skin and mucous membranes[5]; irritation of the skin and rendering of the fingers so tender that it was difficult to pick up a pin[8]; chest pains, fever and severe asthmatic symptoms[2]; development of a supersensitivity "so that it is almost impossible to work even carefully with diazomethane without being subjected to attacks of asthma and fever"[1]. Arndt described it as "an especially insidious poison"[1]. While these warnings, included in a technical journal, would seem to be adequate, a full realization of the serious character of the toxic effects produced by diazomethane apparently does not exist.

Diazomethane is a very unstable, odorless, yellowish gas which is of great usefulness chemically as a methylating agent. Because of its high degree of chemical activity it not only presents a toxic hazard but is explosive as well. For this reason it is generally not employed in its gaseous form, but is dissolved in ether or benzene in which it is readily soluble. Some details of its nature and uses may be found in the article by Sunderman *et al.*[10].

Case Report. H.W., a 28 year old, white male chemist, working in a research institute, was engaged in an investigation of ergothioneine, a procedure which involved the employment of various chemical agents, including phosphorus pentachloride, hydrogen chloride, acetyl chloride and diazomethane. On November 25, 1948, he worked with these substances in a trial run of a preliminary step in his project. On December 2 he repeated the process on a much larger scale. Reluctant to leave a distillation operation which was in progress, he ate his lunch in the laboratory. It consisted of a rather greasy hamburger sandwich, which might have some significance because of the fat solubility of diazomethane. The patient inadvertently inhaled the gases produced in the course of his experiment, although he was working under a laboratory hood. During his activities he became aware of a tickling discomfort in the throat, and began to cough. The cough was short, hacking, dry and persistent. On December 3 he worked in the laboratory as usual, but went home early because of fatigue, substernal soreness and the cough which had continued without cessation from its onset. That night he called his physician to whom he mentioned the nature of his research and the recent exposure to chemical irritants. At that

time physical examination was negative. The oral temperature was 102.4° F. He was given 300,000 units of procaine penicillin G in aqueous suspension intramuscularly. The following day, December 4, he took several doses of aspirin because of a severe headache, and seemed improved. When re-examined by his physician in the early evening he revealed a few fine crepitant rales at the base of the left lung; the oral temperature was 100.2° F. In general his condition seemed considerably better. He was given a second dose of penicillin. However, during the night he became quite dyspneic and his cough was even more harassing than before. At 3 a.m. on December 5, after a brief episode of chilliness, his temperature rose to 104° F. At 7 a.m. his physician found signs of what he believed to be pneumonitis at the base of the left lung.

I first saw the patient at noon on December 5. The history revealed the fact that he had inhaled the chemicals mentioned above. The irritating nature of phosphorus pentachloride, hydrogen chloride and acetyl chloride was fully appreciated. However, the patient offered no information as to the character of diazomethane, of which neither his physician nor I had any knowledge At this examination there was rapid, gasping respiration, harassing short cough and some degree of apprehension. There was also marked flaring of the alae nasae and retraction of the intercostal, suprasternal and supraclavicular spaces on inspiration. Signs suggestive of pneumonitis involving the left lung were again present. These consisted of slight to moderate impairment of the percussion note, bronchovesicular breath sounds and numerous fine and coarse crepitant rales. A few fine crepitant rales were also present below the right clavicle. The temperature was still 104° F., the cardiac rate 90 and the respiratory rate 30 per minute. The blood pressure was 128/80. At 1:35 p.m. the patient was admitted to Jewish Hospital.

At 4 p.m. it was found that dullness was present throughout the right upper lobe and much of the middle lobe. In the same areas there were also bronchial breath sounds, coarse and fine crepitant rales but little change in vocal resonance. The patient complained of being unable to fill his lungs with air. Moderate cyanosis was present in spite of oxygen therapy. It was increasingly evident that we were dealing with no ordinary pneumonic process. Although a second consultant who examined the patient was of the opinion that this was a fulminating pneumonia, probably pneumococcal complicating an earlier virus pneumonitis, attempts to discover the possible role of diazomethane as the cause of a chemical pneumonia were continued. However, the day being Sunday, few sources of information could be reached and none of these could clarify the question. It was not until the morning of December 6 that we learned that diazomethane was in all probability the cause of the patient's symptoms.

There was little change in the pulmonary signs from the evening of December 5 until the patient died at 4:45 p.m. on December 6, about 100 hours after definite exposure to diazomethane. However, the cardiovascular manifestations were of considerable interest The blood pressure at 1:35 p.m. on December 5 was 134/80 and the cardiac rate was 100 per minute. At 4:30 p.m. the blood pressure was 146/80 and the cardiac rate 136 per minute. At 8:30 p.m. the readings were 170/88 and 140 respectively; at 1 a.m. on December 6, 180/90 and 136; at 7 a.m. 170/90 and 176, from which point on the blood pressure dropped slowly throughout the day while the cardiac rate maintained a level in excess of 170 per minute until death occurred. From 1 a.m. on December 6 the respiratory rate averaged 44 per minute Except for one instance, following sponging the temperature never fell below 104°, rising to 106° terminally. All measures to control the progressive shock, anoxia and hyperpyrexia were of no avail. It is worthy of note that frank pulmonary edema was never evident by physical signs.

Other manifestations which occurred included mental confusion which first appeared late in the evening of December 5; muscular twitchings which seemed to respond to 5% intravenous dextrose infusion; coma which developed quite suddenly at 8 a.m. on December 6; vomiting of a small amount of brownish material, strongly positive for occult blood at noon on December 6, and the vomiting of about 750 cc. of partly coagulated blood terminally.

Treatment consisted of oxygen therapy; sedation for the cough, restlessness and substernal distress by means of small subcutaneous doses of morphine sulphate; ice caps and alcohol sponges for the hyperthermia; penicillin, combined sulfadiazine and sulfamerizine, and dehydrostreptomycin. Intravenous or hypodermic dextrose in normal saline solution or in distilled water, in 5% concentration, were given as the state of the patient's fluid balance seemed to indicate. Blood plasma, whole blood transfusion and adrenal cortex extract were employed to combat the state of shock.

The laboratory studies were largely limited by the patient's critical status and brief illness. A blood count on December 5 revealed 14.5 gm. of hemoglobin with 4.5 million erythrocytes. The leukocytes numbered 11,300

of which 83% were neutrophils, 6% were monocytes and 11% lymphocytes. Of each 100 neutrophils 54% were filamentous forms and 46% were nonfilamentous. On December 6 there was a marked leukocytosis, over and above obvious hemoconcentration. While the red blood cell count was 5.6 million, with a hemoglobin reading of 15.5 grams, the leukocytes were 23,600 in number, the differential count being approximately that of the preceding day. The urine was typical of a patient suffering from a very acute febrile reaction, the specific gravity being 1.035, with 4 plus albumin, 1 plus acetone and 0.5% of sugar (apparently due to therapy) present. There were also some hyaline and occasional granular casts. The blood sugar, after therapy was begun in the hospital, was 366 mg. and the urea nitrogen was 17 per 100 cc. of blood. A single blood culture showed no growth.

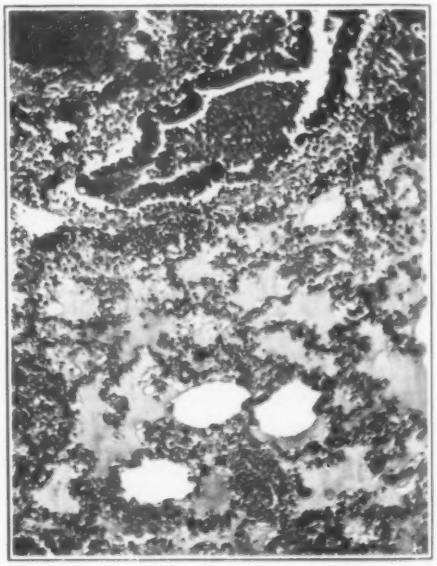

FIG. 1. Section through Wall of Trachea (x 100).
FIG. 2. Section of Lung and Bronchiole (x 100).

AUTOPSY (by Dr. Benjamin Gouley, chief coroner's physician, 19 hours after death). The salient gross features were in the respiratory system. Both *lungs* were large and bulky, the right weighing 850 gm. and the left 800 gm. On section they revealed deep, red, moist parenchyma studded with numerous tubercle-like gray points. Many of these under pressure were seen to be semi-liquid, exuding small points of pus. There were no gross consolidations in either lung. The *trachea*, the two main bronchi and all of the bronchial branches showed a deep red, swollen velvety surface, covered in many places by a thin layer of catsup-colored exudate.

The *myocardium* was pale, brown, soft and cloudy. The *liver* weighed 1550 gm. and appeared somewhat small for the size and age of the patient. There was marked mottling of the surface, in many irregular areas having a pale yellow color in contrast to more congested dark brown segments. Section revealed lobules with pale yellow centers surrounded by red rings. There was a greasy aspect to the cut surface.

The *esophagus* showed a swollen, dark red, in places almost black mucosa, particularly in the lower half where there were surface erosions and necrosis of surface epithelium. The *stomach* was moderately dilated, its mucosa somewhat congested, but showed nothing of the striking change seen in the esophagus. The congestion was most marked at the cardia, fading rapidly toward the fundus. It contained 300 cc. of dark, almost black fluid. The *duodenum* likewise showed mucosal congestion but no ulceration.

The *thymus* was enlarged and cellular for the patient's age level. While fatty tissue was present, there were numerous islands of grayish-red and red thymic tissue throughout.

The *brain* revealed on section a rather

striking spotting of red throughout the white matter, seen almost equally in all lobes of the cerebrum. The cortex showed nothing of note

HISTOLOGIC EXAMINATION of the *trachea* and main stem *bronchi* showed the ciliated epithelium to be almost entirely lost and the mucosa markedly thickened by edema and congestion. There was enormous engorgement of capillaries and small veins. The tissue forming the background of the mucosal structure

FIG. 3. Section of Myocardium (x 100).
FIG. 4. Section of Brain (x 100).

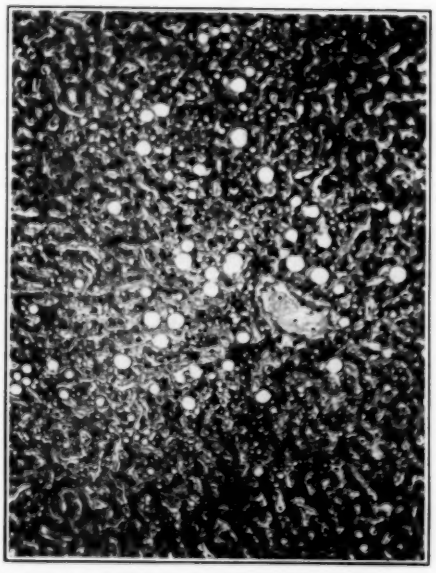

FIG. 5. Section of Kidney (x 100).
FIG. 6. Section of Liver (x 100).

was swollen with edema, some fields showing necrosis. There was a heavy cellular infiltration into the mucosa consisting of polymorphonuclear cells and of various types of the monocytic series. The bronchial muscle fibers were swollen and pale, many appearing to be in the early stage of coagulation necrosis. The glands of the bronchial mucosa were distended with secretion and showed heavy cellular infiltration.

In the *lungs* there was widespread acute congestion. The site of each bronchiole was marked by an intense inflammatory reaction, loosening or desquamation of the bronchiolar epithelium and filling of the lumina with cellular debris. Under the displaced epithelium there were dense cellular infiltrations of polymorphonuclear and other leukocytes which extended out into the adjacent lung structure, constituting an acute peribronchiolar pneumonia with breakdown of alveolar walls and filling in to form small coalescent alveolar abscesses. The small blood vessels were greatly congested and frequently showed a perivascular collar of leukocytes.

Sections from the interventricular septum of the *heart* showed interstitial edema of the myocardium. Many groups of muscle fibers showed hyalinization, a "curling" misshaping, swelling or acute atrophy and, in some fields, infiltration by leukocytes. There was intimal thickening in the left coronary artery.

The *brain* disclosed occasional foci throughout the white matter where the original structure had disappeared or was in process of doing so. These areas took a pale reddish stain and gave the appearance of fibrinous necrosis. However, there was no hemorrhage into these acutely necrotic areas. Many small blood vessels, venules and possibly some arterioles were filled with hyaline thrombi completely occluding the vessels.

There was marked congestion of the *renal* glomeruli. While the capsules were distended and, in many glomeruli, showed slight to moderate thickening, there was no regular inflammatory reaction. All of the proximal convoluted tubules showed marked epithelial swelling, almost closing the lumina in many instances and constituting a marked nephrosis. In contrast to this the distal tubules were well preserved although they contained much albuminous and hemoglobinuric material.

The inner third to half of each *liver* lobule showed much fatty change, whereas the outer half was markedly congested. In the interlobular capillaries were seen a greater number of leukocytes than normal. There was an occasional swollen Kupffer cell and slight to moderate infiltration of leukocytes in the perilobular connective tissue. The nuclei of the hepatic cells were in general well preserved, except in the areas of marked fatty degeneration.

In the upper *gastrointestinal tract* the squamous epithelium of the esophagus was generally intact but the mucosa was swollen with distended capillaries, marked interstitial edema and leukocytic infiltration. The muscular layers all showed some swelling due to interstitial edema. Unfortunately, sections from the stomach were lost. The duodenum showed acute focal necrosis of the epithelium and a marked inflammatory reaction in the mucosa and submucosa.

The *adrenals* revealed medullary edema and focal degeneration in the cortex. There was hyperplasia of the *splenic pulp* with congestion and hemorrhage.

The *pathological diagnosis* was acute ulcerative tracheobronchitis, bronchiolitis and bronchiolar pneumonia, with secondary toxic changes in the heart, kidney and liver; acute esophagitis; acute gastritis; acute duodenitis.

Discussion. For a specific toxicologic diagnosis it would, of course, be desirable to have identified the presence of diazomethane in the blood stream or the tissues of the patient. However, the great instability and the high reactivity of the poison as well as the time which elapsed between exposure and the conclusion that diazomethane was the responsible agent, a matter of some 72 hours, made such a procedure entirely unfeasible. Furthermore, there is apparently no test available at this time by which such an identification could be made.

Sunderman's patient[10] gave an unquestionable history of hay fever and asthma. The manifestations which he exhibited resembled those of bronchial asthma so strongly that therapy early in the course of that patient's illness was directed along those lines. In the present case there had never been any allergic phenomena during the patient's lifetime. The clinical appearance was that of a fulminating pneumonia. The reason for the difference in the manifestations is open to question. The degree and duration of exposure to diazomethane is without doubt of considerable importance. Of great moment,

also, is the mode of action of this agent. Due to its high reactivity it combines readily with the tissues. In the present case it is probable that the intense involvement of the tracheobronchial tree was due to direct contact with inhaled gas while the pronounced gastrointestinal changes were possibly similarly due to contact with the diazomethane-contaminated sandwich eaten while the patient worked in the laboratory. It is of great interest to note that there was no complaint of dysphagia at any time.

Flury and Zernik[4] state that there is a slow reaction of diazomethane with water to form methyl alcohol, with the liberation of nitrogen. Oxidation of methyl alcohol produces formaldehyde. Lehmann and Flury[7] point to the formation of formaldehyde and formic acid from methyl compounds, such as diazomethane, and include these substances among the true enzyme poisons. Axmacher[3] has found that diazomethane inactivates zymase as well as carboxylase in yeasts. From these statements it seems probable that it has a similar effect on enzyme systems in animal tissue.

In areas such as the trachea the action of diazomethane appears to be corrosive, at least in part. However, its influence on tissues where there has been no direct contact cannot be of this character. Landsteiner and DiSomma[6], who employed diazomethane as a sensitizing agent in order to produce allergic effects, noted that the reactivity of this poison is so great "that it doubtless combines with substances of the animal body rapidly after administration and for this reason the spread of sensitization can hardly be ascribed to the distribution of the exciting substance itself but to transportation of some sort of conjugate (such as methylated protein) or, perhaps, antibodies".

In a discussion of the industrial hazards presented by organic chemical synthesis Watrous[11] points out that the active agents used to attack and modify the structure of organic compounds are, by their very nature, exceptionally able to modify the organic compounds of the human body, thus producing highly poisonous effects. Watrous also notes that the intermediate compounds in most organic syntheses are often characterized by the readiness with which they enter into chemical combination with other organic matter; they are active. This frequently confers toxic properties of great variety upon them. Of great importance is the fact that any investigator who works with diazomethane, or any other agent such as Watrous describes, is employing a powerful and deadly chemical. It behooves those who supervise laboratory procedures to be aware of the dangers inherent in the activities of their students or assistants and to give full and adequate emphasis to those dangers when any hazardous project is undertaken.

Summary. A report of the clinical features and autopsy findings in a case of poisoning by diazomethane has been presented. Diazomethane is a highly toxic agent which appears to have a corrosive action upon tissues with which it is in direct contact. In addition, it appears to produce sensitizing effects so that part of its insidious character lies in allergic reactions which may arise in any area or organ of the body not directly exposed to it. The clinical picture thus produced may resemble bronchial asthma or a fulminating pneumonia. The great caution necessary on the part of those who work with this agent is clearly evident and should be stressed whenever its use is contemplated.

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THE DIAGNOSTIC SIGNIFICANCE OF "BURR" RED BLOOD CELLS*

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In the course of the routine review of blood films a peculiar red cell, measuring about 7.5 micra or less in diameter and having one or more large spiny projections along its periphery, was seen from time to time. The impression was gradually gained that this form represented an entity which, although occasionally encountered in other conditions, occurred most frequently in uremia, carcinoma of the stomach, and peptic ulcer with bleeding. We have found that this peculiar poikilocyte, which we have designated "burr" cell, often offers the first clue to diagnosis. Experience has taught us to use "burr" cells as valuable signposts in the etiologic evaluation of anemias. This study was undertaken to test the validity of what, to the present time, had been simply an impression, and to determine the frequency with which "burr" cells occur in both normal and abnormal states.

Material and Methods. Blood films from 75 cases of uremia, 50 cases of carcinoma of the stomach, and 50 cases of bleeding peptic ulcer were studied. The control series was made up of 2 groups. The first consisted of 100 consecutive blood films obtained from patients entering the medical wards of the hospital for miscellaneous conditions and having no hematologic aberrations, while the second was made up of 100 similarly obtained bloods which showed some hematologic abnormality such as anemia, leukocytosis, poikilocytosis, and so on.

The diagnosis of uremia was made on the basis of azotemia together with one or more of the clinical findings of nausea, vomiting, irritability, lethargy, uremic frost, pericarditis, and coma. All patients had blood creatinine levels of 3 mg. per 100 cc. or over and nonprotein-nitrogen levels of 70 mg. per 100 cc. or more. Of the 75 patients whose bloods were studied, 71 died. The blood pressure was 150/90 or over in 62 (82%) of these cases.

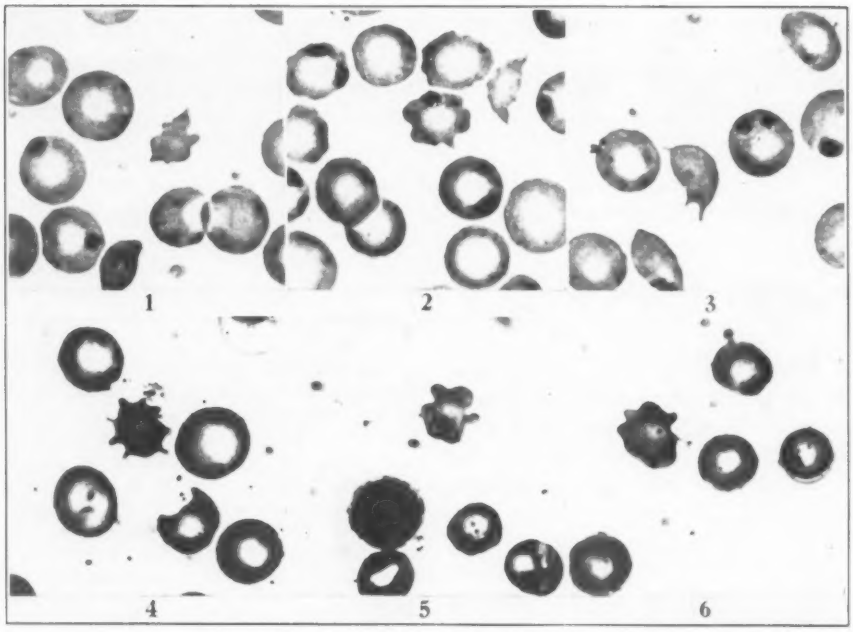
The diagnoses of carcinoma of the stomach and bleeding peptic ulcer were substantiated by gastroscopy, Roentgen-ray, and, or, surgery.

One thousand red blood cells were counted on each dry blood film. In addition, 25 wet preparations were made; 15 from the blood of uremic patients, 5 from patients with carcinomas of the stomach, and 5 from patients with bleeding peptic ulcers, in order to study the appearance of the cells in a relatively unmodified state.

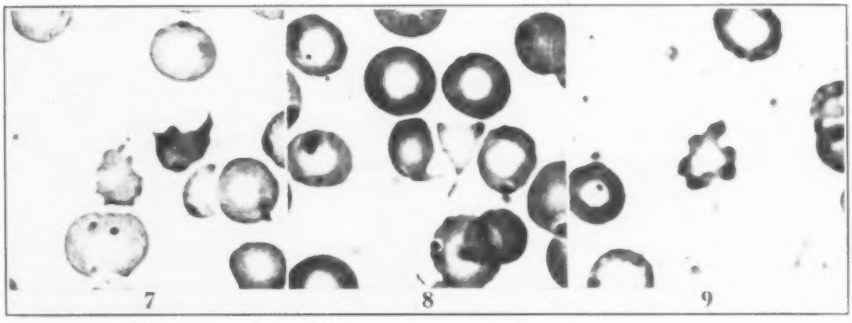
We were particularly interested in determining whether the "burr" cell was a form of poikilocyte or a crenated cell. The appearance and frequency of occurrence of the "burr" cell in the wet preparations leaves little doubt but that these cells represent a preformed poikilocyte and not a crenated cell. There are occasional "burr" cells, however, which are difficult to differentiate from crenated cells (Figs. 2 and 9).

The "burr" cell is a mature erythrocyte about 7.5 micra or less in diameter, which has one to several spiny projections along its periphery. We have

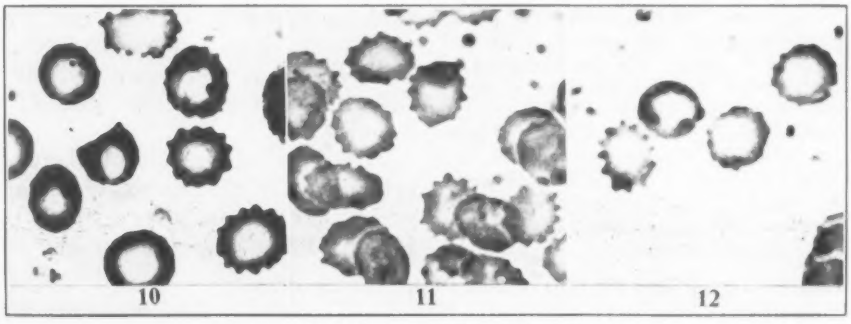
* Aided by a grant from the Wilson Laboratories, Chicago, Illinois.



Figs. 1 to 6. Various kinds of "Burr" cells.



Figs. 7 to 9. Various kinds of "Burr" cells
(Cont'd)



Figs. 10 - 12. Crenated Erythrocytes.

chosen to call it "burr" cell because of its resemblance to the prickly envelope of a burr. "Burr" cells differ from crenated red cells in that the latter have many, fairly symmetrically arranged small spiny projections which often occur on the surface as well as the periphery; and whereas crenated cells occur in groups, sometimes more in one area than another, "burr" cells are fairly evenly scattered throughout the blood film. In the enumeration of "burr" cells for this study only those were counted which were untouched by adjacent cells and which were located in fields in which no crenated cells were present.

Of the 75 cases of uremia, 54 cases (73%) showed "burr" cells. The range of incidence of the "burr" cell in this group was 0.1% to 1.5% (1 to 15 "burr" cells per 1,000 red cells counted). No correlation existed between the incidence of "burr" cells and race, sex, age, height of blood pressure, anemia, color index, or the levels of the non-protein-nitrogen or creatinine.

Of the 50 patients with carcinoma of the stomach, 34 (68%) had "burr" cells. The percent incidence of the "burr" cell in this group was from 0.1 to 3.7 (1 to 37 "burr" cells per 1,000 red blood cells counted). No correlation was demonstrable between the incidence of "burr" cells and race, sex, age, and the anemia or the color index.

Of the 50 patients with bleeding peptic ulcers, 27 (54%) showed "burr" cells. The range of the incidence of "burr" cells in this group was 0.1% to 1.2% (1 to 12 "burr" cells per 1,000 red cells counted). In this series there were 37 patients with duodenal ulcers, 11 with gastric ulcers, and 2 with marginal ulcers. No correlation existed between "burr" cell incidence and the site of the ulcer, race, sex, age, anemia or the color index.

On the 100 blood films of the control group which revealed miscellaneous non-hematologic diseases, no "burr" cells were found; while in the 100 preparations obtained from patients showing some hematologic aberration, 21 had "burr" cells. The 21 cases were made up of the following conditions:

Azotemia	3
Organic Heart Disease	1
Organic Heart Disease with Failure	2
Carcinoma—Rectum	2
Carcinoma—Gastro-intestinal—site unknown	2
Carcinoma-stomach	1
Pernicious Anemia	1
Pernicious Anemia—with Carcinoma of Stomach	1
Malnutrition	1
Tuberculosis	1
Thyrotoxicosis	1

Discussion. This study failed to reveal the pathogenesis of the "burr" red cell and did not elucidate the common denominators among uremia, carcinoma of the stomach, and bleeding peptic ulcer. Severity of anemia, level of color index, amount or duration of bleeding, degree of nitrogen retention, age, sex and race were all taken to be insignificant. Hypoproteinemia and blood in the intestinal tract may play a part. Dehydration is apparently not a significant factor, as we have not commonly observed "burr" cells in severely dehydrated diabetic patients in acid-

TABLE 1. OCCURRENCE OF "BURR" CELLS IN THE CONDITIONS STUDIED

Condition	Number of Cases	Incidence of "Burr" Cells		Range of Incidence of "Burr" Cells
		Number	Percent	
Normal	100	none	0	
Various hematologic abnormalities*	100	21	21	—
Uremia	75	54	73	0.1%–1.5%
Carcinoma of stomach	50	34	68	0.1%–3.7%
Bleeding peptic ulcer	50	27	54	0.1%–1.2%

* These include an undetermined but probably small number of cases of uremia, carcinoma of the stomach, nephritis, and so on.

osis. It is interesting that in the control group of miscellaneous hematologic conditions the most frequent common denominator was renal impairment.

Summary. In the peripheral blood of patients with uremia, carcinoma of the stomach, and bleeding peptic ulcer, peculiar poikilocytes frequently occur which we have designated as "burr" cells.

"Burr" cells occurred in the bloods of 73% of the patients with uremia, 68% of carcinoma of the stomach, and 54% of bleeding peptic ulcers.

"Burr" cells are very rare in normal bloods (none in 100 control cases), but occur in conditions other than the above mentioned—though their presence should always suggest additional renal involvement.

Conclusion. "Burr" cells are valuable sign posts in the study of anemias.

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RECENT ADVANCES IN PARENTERAL FLUID THERAPY

With Ammonium Chloride and Potassium

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THE field of parenteral fluid therapy has been developed chiefly during the past 25 years. General progress in the fields of biochemistry and physiology as well as more specific investigations on fluid and electrolyte metabolism have supplied a basis for the rational use of such solutions as saline, glucose, sodium bicarbonate, and sodium lactate in the treatment of dehydration and acid-base disturbances. The literature contains a number of excellent reviews which summarize these basic studies and therapeutic procedures[1,10,36,78]. During the past few years a number of other substances, namely, ammonium chloride, potassium salts, protein digests and whole blood have assumed importance in parenteral therapy. It is the purpose of the present paper to review the advances in the fields of ammonium chloride and potassium therapy.

Potassium. Until about a decade ago, it was generally assumed that such ions as sodium and chloride were extracellular, that others such as potassium and magnesium were predominantly intracellular, and that there was little exchange of these various ions across the cell wall. The work of Hastings, Eichelberger and their associates[23,48,49,70] on the calculation of the extracellular and intracellular phases of muscle tissue were based on such assumptions and the results of their work substantiated these assumptions. However, Hastings carefully pointed out at this time that these assumptions held under essentially normal physiological conditions. During the past decade there has accumulated increasing

evidence that the cell wall is not as impermeable as it was formerly thought to be and that under unusual environmental or pathological conditions, intracellular electrolytes may pass across the cellular membranes and, on the other hand, that under appropriate therapeutic conditions such intracellular components may be restored.

Some information concerning the normal distribution and metabolism of potassium in the body is necessary before we consider the deviations in disease and the therapeutic measures necessary to correct these deviations. As for any other component of the body, it is important to determine the relationship between the extent of storage and excretion throughout a wide range of various levels of intake, and to ascertain the influence of various physiological variables upon this relationship.

Distribution of Potassium in the Human Body. The potassium content of the human body has been estimated variously as anywhere between 0.11 to 0.35%[95]. This would mean that an individual weighing 70 kg. would contain between 77 and 245 gm. or between about 2000 to 6000 m.Eq. of potassium. Myers and Mangun[80] found that the pectoralis major muscle contained an average of 352 mg. potassium per 100 gm. tissue; if a similar estimate is made of the potassium content of other tissues, then the total content in a 70 kg. adult would be about 245 gm.

The normal concentration of potassium in the blood serum of man is about 16 to 20 mg. per 100 cc. or about 4 to 5 m.Eq. per liter. Thus, in a series of 10 normal individuals Kramer and Tisdall[61] found the serum potassium to range from 19.2 to 20.0 and average 19.6 mg. per 100 cc. Hald and Eisenman[46] observed a somewhat greater variability in a series of 16 normal individuals; the concentration ranged from 3.4 to 6.5 and averaged 4.6 m.Eq. per liter. Recently, in a series of flame photometric determinations on 106 normal individuals, Marinis and his associates[72] found the values to range between 3.6 and 6.2 m.Eq. per liter. Of these values 75% fell between 4.2 and 4.8 m.Eq. per liter and 93% between 3.9 and 5.1 m.Eq.

The concentration of intracellular potassium cannot, except in the case of the red blood cells, be determined directly. However, the concentration of potassium in the red cell can also be determined indirectly. In the series of 16 individuals previously referred to, Hald and Eisenman found the concentrations of potassium in the red cell to range from 72 to 102 and average 83 m.Eq. per liter or about 125 m.Eq. per liter of intracellular water. In order to calculate the intracellular potassium content of other tissues, it is necessary to determine the potassium content of the whole tissue, then from this value, subtract the amount of potassium in the extracellular compartment of the tissue. The latter is calculated on the assumption that the extracellular fluid compartment comprises about 15 to 20% of the tissue and that the concentration of potassium in the extracellular fluid is the same as that in the plasma, but corrected for the Donnan effect. Katz[55] found a concentration of 320 mg. and Myers and Mangun[80] 352 mg. of potassium per 100 gm. of human muscle. This is of the same order of magnitude as that recently reported by Mudge and Vislocky[79], namely, 82 to 88 m.Eq. per kg. of fat-free tissue. These values yield a concentration of about 150 to 160 m.Eq. per liter of intracellular water.

Metabolism of Potassium. The normal daily potassium intake and excretion of an adult is about 3 to 4 gm. or 75 to 100 m.Eq.[26,95]. Practically the entire excretion takes place through the urine and feces, although there is evidence that potassium is also eliminated

through the perspiration. Estimations of the excretions are, however, usually based on urine and stool analyses; it is found that about 10 to 20% of the potassium is excreted in the stools, and the remainder in the urine. These statements may be illustrated by reference to specific studies. For example, Bassett and his associates[4] found, in one instance, that on an average daily intake of 3.79 gm., the excretion was 3.19 gm.; of this amount 14% was in the stools. In their series of classical studies on chemical growth in children, Macy and her co-workers[68] found that, in children ranging from 4 to 12 years of age, the excretion ranged from about 90 to 96% of the daily intakes, 2.5 to 3.5 gm. The fecal excretion ranged from 8 to 16% of the total excretion.

There appear to be only a few studies which indicate the minimal intake of potassium that is necessary on a complete and adequate diet to keep the body in potassium balance. Fasting adults who receive water may excrete daily from 30 to 76 m.Eq. (1.2 to 3.0 gm.) of potassium[22, 109]. Tarail and Elkinton[103] found that the daily loss of potassium was of about the same order, 49 to 53 m.Eq., when a normal individual was on a calorically adequate but practically potassium free diet. On adequate daily diets containing 99 to 116 m.Eq. of potassium per day, 2 normal individuals showed balances ranging from −30 to +13 m.Eq. per day. It would be of value to obtain additional balance data in normal individuals at intermediate potassium intakes.

Loss of Intracellular Potassium in Disease. In 1933, Butler, McKhann, and Gamble[9] observed that infants who had been suffering from severe diarrhea excreted, during the first 24 hours after being placed on glucose and saline, more potassium than could be accounted for on the basis of tissue destruction, as measured by the excretion of nitrogen. The losses of intracellular water, calculated on the basis of nitrogen excretion, were less than those calculated on the basis of the amounts of potassium excreted. These findings indicated that potassium and water were leaving the cells.

These findings were established again by Darrow[18] in 1946. When infants with diarrhea were admitted to the hospital and placed on parenteral fluid therapy consisting of solutions of saline, lactate, glucose and of blood, there occurred marked negative potassium balances. Correction for the amount of potassium resulting from tissue breakdown showed that potassium was migrating out of the cells. When potassium chloride was added to the diet in the next metabolic period, a marked positive balance of potassium resulted. For example, in one case, the potassium balance was −8.43 m.Eq. during a 39.5 hour metabolic period on the usual parenteral fluid therapy. When 2 gm. of potassium chloride were given during the next metabolic period of 49.5 hours, the potassium balance was positive to the extent of 23.1 m.Eq. We shall consider presently the other significances of this uptake of potassium, but it may be noted here that such uptake was further indication that the cells had been depleted of potassium.

Darrow's observations and penetrating inferences[18,19] have been followed by a number of other reports which demonstrate the passage of potassium across cellular membrances in other diseases or in marked physiological derangements. Danowski and his associates[15] have shown that in familial periodic paralysis the onset of episodes of paralysis is associated with a transfer of potassium from the extracellular to the intracellular phase, resulting in a sharp decrease in the concentration of potassium in serum and presumably also in the extracellular phase. Elkin-

ton, Tarail and Peters[24] have observed that occasionally in patients with renal insufficiency and hyperpotassemia, potassium may be taken up by the cells. It had also been shown that in animals, diets low in potassium[32, 50, 77], injections of desoxycorticosterone acetate[20,29], estradiol benzoate or testosterone propionate[76] cause a reduction in the potassium content of muscle.

In the clinical conditions which we mentioned above, the interchanges of intracellular potassium were demonstrated indirectly by balance studies. There are, however, a few direct analyses of the potassium content of muscle which support these conclusions. Darrow reported that in babies dying of diarrhea the potassium content of muscle was about 40% less than that of normal muscle[18]. Mudge and Vislocky[79] analyzed biopsy specimens and found that the contents of potassium in the muscle of 3 patients with renal acidosis were 74.5, 69.1 and 66.1 m.Eq. per kg. of fat-free tissue. In 3 patients with gastric alkalosis, the concentrations ranged from 51.4 to 85.7 m.Eq. per kg. These were lower than the values from 3 normal individuals, namely, 81.9, 87.0 and 88.0 m.Eq. per kg.

Relationship Between Sodium and Potassium Interchanges. A number of investigators have shown that an interrelationship exists between sodium, potassium, chloride and bicarbonate ions. When the muscle potassium in rats was decreased by feeding a diet low in potassium or by injecting desoxycorticosterone acetate, the concentration of intracellular sodium rose[21]. Simultaneously, the concentration of bicarbonate in the extracellular phase (plasma) rose and that of chloride declined. When acidosis was produced, the intracellular sodium increased.

In general, then, serum bicarbonate varied directly with the intracellular sodium and inversely with the intracellular potassium. Fox and Baer[31] found that when the hind leg of a mouse was injured by tourniquet trauma or by scalding, the injured leg lost a considerable amount of potassium but gained sodium. Conversely, the opposite uninjured leg lost sodium but gained potassium. The direct analyses of Mudge and Vislocky[79] on human muscle show that in acidosis and alkalosis the concentration of intracellular sodium rises as the concentration of intracellular potassium decreases. Thus, whereas the normal concentration of sodium ranged from 2 to 14 m.Eq. per liter of intracellular water, concentrations from 17 to 40 m.Eq. per liter were obtained in acidosis and from 13 to 74 m.Eq. per liter in alkalosis.

The interdependence between potassium, sodium and bicarbonate ions has also been observed clinically. A few instances of this may be cited in illustration. McQuarrie, Johnson and Ziegler[67] reported a case of Cushing's disease which had a CO_2 combining power of 112 vols. per 100 cc. and a pH of 7.55 to 7.60. The concentrations of the other ions (as read from the author's Chart) were as follows per liter: Na^+, 155 m.Eq.; K^+, 2 m.Eq.; HCO^-_3, 42 m.Eq.; Cl^-, 88 m.Eq. In another instance of Cushing's disease, Willson, Power and Kepler[108] observed the following ionic concentrations per liter: Na^+, 137 m.Eq.; K^+, 2.2 m.Eq.; HCO^-_3, 46 m.Eq.; Cl^-, 78.0 m.Eq. Recently, it has been shown that after operation, hypopotassemia may occur accompanied by an increased concentration of bicarbonate ion in the serum[53,64,66,83].

Hypopotassemia and Hyperpotassemia. As we have already seen, balance studies can yield a fairly precise idea concerning the existence of intracellular potassium deficits. Since only about 10 to 20% of excreted potassium is found in the stools, determinations of urinary excretion of potassium may

also serve as a valuable, though only approximate, guide of undue losses or of storage of potassium in the body. However, since the blood is most readily available for analysis, it is of interest to determine the extent to which the level of potassium in the serum can serve as an index of intracellular potassium deficits.

A lowered concentration of serum potassium has been found in patients recovering from diabetic acidosis[35,52,65,82,104], in infantile diarrhea[91], alkalosis due to intestinal obstruction and vomiting[5], congenital alkalosis with diarrhea in early life[17,38], periodic paralysis[2,27,28,40,41,99,105], nephritis[8,87,96,103] and in postoperative states[53,64,66,83]. It will be recalled that most normal values for the concentration of serum potassium range between 4 and 5 m.Eq. In familial periodic paralysis, values of between 2 and 3 m.Eq. per liter have often been recorded. Logsdon and McGavack[65] have reported a value of as low as 1.0 m.Eq. in a patient with diabetic acidosis who developed respiratory paralysis and died. In renal insufficiency, the concentration of serum potassium may be either low, normal or high. Elkinton and his associates[24] found that of 26 patients with renal insufficiency, 4 had serum potassium concentrations less than 3.5 m.Eq. per liter, 23 had concentrations between 3.5 and 6.4 m.Eq. per liter, and 11 showed values greater than 6.4 m.Eq. per liter.

The concentration of potassium in the serum represents the resultant of several processes, namely, introduction of potassium into the organism, liberation from or storage in the tissues, and excretion through the urine or stools. It does not necessarily follow, therefore, that a low concentration of serum potassium will be obtained when there is a low store of intracellular potassium. In the 6 cases of infantile diarrhea studied by Darrow[18], the initial potassium concentrations were 7.4, 6.7, 5.0, 5.5, 4.8, and 3.7 m.Eq. per liter. Some of these results are high and, as will be seen later, may indicate renal impairment. Yet these patients had been losing potassium, continued to do so when placed on saline-glucose therapy, and presumably, therefore, had intracellular potassium deficits. Rapoport and his associates[88] found that when the acidosis of infantile diarrhea was corrected by the administration of sodium bicarbonate, there occurred marked decreases in the concentration of potassium, as well as calcium and phosphorus. Decreases of the potassium concentration to between 2 and 3 m.Eq. per liter were common and occasionally values below 2 m.Eq. per liter were obtained. They interpreted this finding to indicate an avid uptake of these ions by the previously depleted tissues. Although Rapoport and his co-workers reported no balance studies, it may be appreciated that his interpretations are in accord with the observations and conclusions later established by Darrow. In the extremely rare condition of congenital alkalosis with diarrhea studied by Darrow[17], low concentrations of serum potassium were obtained occasionally. The metabolic results showed that there was an excessive excretion of potassium in the urine and stools, and suggested that the initiating force for this excretion was the driving out of potassium from the cells and its replacement by sodium.

The genesis of hypopotassemia in diabetic acidosis has been investigated by Danowski and co-workers[16]. The classical studies of Atchley, Loeb, and their associates[3] had shown that during the development of insulin-withdrawal acidosis, there was a marked diuresis of large amounts of potassium, nitrogen, phosphorus and other elements. In one case studied by these investigators, there was a net loss of

385 m.Eq. potassium during a 4 day period of acidosis. This is about 10% of the total store in the body. Danowski and associates[16] found that when the conventional therapy of insulin, glucose, and saline was administered to patients with diabetic acidosis, there occurred a rather sizable increase in the extracellular fluid volume of the body while at the same time potassium continued to be excreted from the body. For example, in a female diabetic weighing 50 kg., 74 m.Eq. of potassium were excreted during a 20 hour period on insulin, saline and glucose therapy. The extracellular fluid volume increased by 4.4 liters or by about 8% of the body weight. The hypopotassemia of post-acidotic diabetes may accordingly be ascribed in part to a continued loss of potassium from the body, and in part to a dilution of the potassium ion as a result of the increased extracellular fluid volume.

The extraordinary depletion of potassium which the cells of the body undergo during the development of diabetic acidosis and treatment with parenteral fluids devoid of potassium is manifested by an equally unusual retention which occurs when potassium is administered to such patients. For example, in the case quoted above, Danowski and associates[16] found that the administration of 505 m.Eq. of potassium during a 47 hour treatment period resulted in the retention of 297 m.Eq. Of this amount, 292 m.Eq. were deposited intracellularly. Howard and Carey[53] note an instance in which they injected 467 m.Eq. of potassium (35 gm. KCl) into a patient with diabetic acidosis in 18 hours; less than 100 m.Eq. of potassium were found in the urine. Tarail and Elkinton[103] showed that, in contrast, normal individuals retained only 5 to 10% of a dose of 250 m.Eq. of potassium.

It has been shown that the glomerular filtration and the renal excretion of potassium may be decreased in patients with renal insufficiency. Whether the concentration of serum potassium in this condition increased or not depends upon a number of factors, namely, the intake of potassium, the extrarenal loss of potassium, the decreased renal excretion of potassium, the change in the volume of the extracellular fluid, and the interchange of potassium between the extracellular and intracellular phases[24]. Certainly it would appear that in those cases in which hyperpotassemia occurs, the factor chiefly responsible is the decreased renal excretion of potassium. Hyperpotassemia of this type does not favor intracellular deposition; of 9 cases studied by Elkinton and associates[24] on daily intakes ranging from 0 to 30 m.Eq., 7 showed losses of intracellular potassium and only 2 showed slight deposition. The occurrence of decreased concentrations of serum potassium in patients with renal insufficiency is to be ascribed chiefly to the fact that although the renal excretion is decreased, the intake is limited because of anorexia, chiefly for foods containing potassium, and losses occur through the gastrointestinal tract.

The hypopotassemia in familial periodic paralysis appears to have an entirely different cause from those described above. It is, of course, well known that hypopotassemia in this condition with accompanying episodes of paralysis is induced by the administration of insulin, epinephrine or carbohydrate[41]. Why such stimuli should produce the hypopotassemia in patients with periodic paralysis but not in normal individuals is not well understood. Danowski and his associates[15] have shown that the episodes of paralysis are associated with small transfers of potassium from the extracellular to the intracellular phase. For example, in 1 patient in whom paralysis was induced by the administration of a potassium

free carbohydrate diet, the serum potassium decreased progressively from 4.3 to 2.2 m.Eq. per liter. The intracellular entrance in several metabolic periods of 5 to 24 hours duration ranged from 5 to 20 m.Eq., approximately equal to a decrease of about 2 m.Eq. per liter in the 15 liter extracellular fluid volume of the patient.

It is abundantly evident from the few examples which we have given that the concentration of potassium in the serum may, but does not necessarily, reflect the stage of depletion or repletion of intracellular potassium. To illustrate and summarize, the serum potassium is not low and indeed may be high in the active stage of infantile diarrhea where the potassium has left and is still leaving the cells. But in the tissue depletion of congenital alkalosis with diarrhea, it may occasionally be low, and in the postacidotic phase of infantile diarrhea, ingress from the extracellular fluid to the depleted cells leads very frequently to decreased concentrations of serum potassium. The hypopotassemia of the postacidotic phase of diabetes mirrors well the extreme cellular depletion in this condition, but the hypopotassemia of familial periodic paralysis is due to some curious fault whereby some of the extracellular potassium, but enough to lower the concentration in the serum, is rather suddenly deposited in the intracellular phase. As we have seen, the situation in renal impairment is somewhat more complex. It may be appreciated that an understanding of the biochemical mechanism underlying the relations of serum and intracellular potassium in each disease is essential for the proper therapeutic employment of potassium.

Clinical Symptoms of Potassium Deficiency. As we have seen, the existence of a potassium deficiency can be ascertained with considerable precision by balance studies and biochemical analysis of the serum. However, opportunities for conducting balance studies are available in only a few hospitals. The precise chemical determination of serum potassium is a painstaking and time-consuming procedure, although the recent use of the flame photometer has facilitated such determinations greatly. It is, therefore, necessary in many instances to judge the existence of a potassium deficiency on the basis of history and clinical symptomatology.

In the earlier stages of potassium deficiency, the patient shows a loss of strength and energy and is listless[64]. Many of the patients are unable to eat adequate amounts of food. This symptomatology is obviously common to a great many conditions and diseases. The manifestations of marked potassium deficiency are more distinctive[53]. Weakness of the extremities becomes marked; flaccid paralysis, sometimes of the ascending or Landry's type, may then ensue. There is rarely any involvement of the trunk or cranial nerves. Weakness of the respiratory muscles is a grave symptom[35,52,65]. The breathing becomes rapid and shallow and the symptoms of gasping for air, namely, use of accessory muscles, retraction of head and neck, dilatation of alae nasi with each respiration, and "fish mouth" type of breathing become evident. There is very little movement of the chest wall and diaphragm. In the absence of prompt potassium therapy, respiratory paralysis and death may ensue.

The changes in the electrocardiogram associated with abnormalities of the concentration of serum potassium have received considerable attention[30, 57,98,101,102,110,111]. Winkler, Hoff and Smith[110] found the following changes upon the intravenous infusion of isotonic potassium chloride into dogs: increase in the amplitude of the T wave at serum potassium concentrations

ranging from 5.0 to 7.8 m.Eq. per liter, depression of the S-T segment at 8 to 10 m.Eq. per liter, intraventricular block at about 10 m.Eq. per liter, disappearance of the P wave at 9 to 11 m.Eq., and cardiac arrest at 14 to 16 m.Eq. per liter. The changes in man parallel, in general, those found in animals. As the serum potassium rises, there is first an increase in the amplitude of the T wave; then a decrease in the amplitude of the R wave with an increase in the amplitude of the S wave. At higher concentrations, there is a disappearance of the P wave, a depression of the RS-T segment and a widening of the QRS complex. There is incomplete accord, however, with regards to the concentrations of serum potassium at which these changes occur. Winkler, Hoff and Smith[111] as well as Tarail[101,102] found that in patients with uremia and concentrations of serum potassium ranging from 6.8 to 8.3 m.Eq. per liter, the most characteristic changes were peaked T waves and an increase in the duration of the QRS complex. Finch and his co-workers[30] observed disappearance of P wave at between 9 and 9.5 m.Eq. per liter and spread of QRS complex at between 9.5 and 10.5 m.Eq. per liter. Stewart and his associates[98] reported 2 cases with concentrations of 10.3 and 10.6 m.Eq. per liter in whom there was disappearance of the P waves and widening of the QRS complexes.

In hypopotassemia, the sequence of electrocardiographic changes is as follows. With moderate decreases, the T wave becomes slightly lower but broader, so that the Q-T interval as a whole is lengthened. As the serum potassium concentration is decreased further, there is first a lowering or inversion of the T wave and then a sagging of the ST segment. With very low levels of potassium (1.5 m.Eq. per liter or less), there is a slow, staircase-like rise to a low late T wave[53].

It must be emphasized that the relationship between the level of potassium and the electrocardiographic changes is only approximate. For example, in a series of patients with diabetic acidosis, Martin and Wertman[73,74] observed that at normal serum potassium levels (4.2— 5.8 m.Eq. per liter), 14 showed a normal amplitude of T waves, 12 a decreased amplitude, and 1 a very low T wave. At serum potassium levels less than 4.2 m.Eq. per liter, 1 showed a normal amplitude of T waves, 1 a decreased amplitude, and 9 a very low amplitude. In a similar series, Nadler and his associates[81] observed an approximate but a statistically significant correlation between the prolongation of the Q-T interval and the decrease in the serum potassium. However, a significant correlation could also be shown to exist between the height of the T wave and the pH of the serum.

It is apparent that the proper use of electrocardiographic changes as an aid in the diagnosis of hypopotassemia or hyperpotassemia must take into account similar changes which may occur in other cardiac conditions.

We may briefly review the chief features necessary for making a diagnosis of potassium deficiency and for instituting potassium therapy. These are: (*a*), an awareness of the various conditions and diseases likely to be associated with this deficiency; (*b*), the presence of muscular weakness and paralysis, particularly those of the respiratory muscles; (*c*), characteristic electrocardiographic changes; (*d*), the concentration of the serum potassium.

Treatment of Potassium Deficiency in Infantile Diarrhea. As a consequence of Darrow's[42] demonstration that infantile diarrhea was characterized by a loss of intracellular potassium, and that this loss continued during the institution of the conventional saline-glucose therapy, he introduced a pro-

cedure which included the use of potassium chloride. Upon admission, the infant received an intravenous injection of whole blood or plasma (10 to 20 cc. per kg. of body weight); food and water by mouth was stopped. An intravenous infusion or subcutaneous injection of a potassium chloride-sodium lactate solution was then started. The composition of this solution, per liter, was as follows: K^+, 35 mM; Na^+, 122 mM; Cl^-, 104 mM; lactate, 53 mM. This mixture could be made conveniently by adding 2 gm. of KCl and 3 gm. NaCl to 250 cc. of M/6 sodium lactate and 500 cc. of water. A dose of 80 to 150 cc. of this solution per kg. of body weight was given during the first 24 hours. In addition, a 5% solution of glucose was given intravenously so as to make a total water intake of 150 to 280 cc. per kg. of body weight. After the first day, and as long as the stools remained watery, 20 to 50 cc. of the potassium chloride mixture were given per kg. of body weight and enough 5% glucose to make a total water intake of 150 to 200 cc. per kg. of body weight. Vitamin B complex and crude liver extract were also administered. Feeding was started and regulated in accordance with the progress of the patient.

It may be seen from the above that during the first day about 2.8 to 5.3 m.Eq. (about 0.2 to 0.4 gm. of KCl) were introduced per kg. of body weight. In his previous balance studies, Darrow[18] had observed that the average daily losses of potassium on the conventional glucose-saline therapy was about 1 to 1.5 m.Eq. per kg. In contrast, 2 infants who were placed on potassium therapy initially showed positive potassium balances of 3 and 8 m.Eq. per kg. of body weight during 4 days and 3.5 days of therapy. These results indicated intracellular deposition of potassium.

It may be readily appreciated that Darrow's studies show a convincing biochemical and physiological justification for the use of potassium chloride therapy in infantile diarrhea. The question arises concerning the extent to which clinical results reflect this rational formulation. Prior to about 1920, it was generally thought that severe infantile diarrhea or, as it is also termed, intestinal intoxication, was a highly fatal condition with a mortality ranging from 80 to 90%. In 1926, Powers[85] reviewed 64 cases which had been treated in New Haven Hospital from 1922 to 1925. Nine had been admitted *in extremis* or had their treatment interrupted by being taken out of the hospital. Of 19 who received no systematic treatment, 14 (70%) died. Thirty-six patients were submitted to a systematic regime which consisted of: (*a*), withdrawal of all food by mouth; (*b*), blood transfusions; (*c*), administration of sodium bicarbonate; and (*d*), intraperitonal, subcutaneous and intravenous injection of Ringer's solution. Feeding was initiated only when toxic symptoms had abated or disappeared, began with very small amounts and was increased gradually in accordance with the clinical status of the patient, until the total caloric requirement was reached in a week or 10 days. On this regime, 12 of the 36 patients (33%) died. In 1933, Karelitz and Schick[54] submitted a plan of treatment which stressed (*a*), a more radical and longer than usual rest for the gastrointestinal tract, and (*b*), the intravenous drip infusion of a glucose-saline or glucose-Ringer solution. The mortality in 53 cases treated by this method was 6 (12%). The average mortality for the preceding 10 years at the same hospital had been 64%. Campbell and Cunningham[12] reviewed 574 cases of non-specific infantile diarrhea. Parenteral fluid therapy consisted usually of subcutaneous administration of normal saline. In severely ill patients,

the fluids were also administered intravenously or intraperitoneally. Of the 574 cases, 283 were dehydrated upon admission; the mortality rate in these was 53.7%. In the 291 which were not dehydrated, the mortality rate was only 2.4%. The overall mortality rate was 27.7%. Smellie[97] studied 500 cases which had been admitted to the Birmingham Children's Hospital (England) for several years prior to 1939. The therapeutic regime consisted of subcutaneous injections of saline, intravenous injections of normal saline, glucose or blood, and withdrawal of food for the first 12 to 24 hours. The overall mortality was 240 (48%). However, when the whole group was subdivided into those who developed parenteral infection after admission to the hospital, those who had such infection at the time of admission, and those who never had any parenteral infection, the mortality rates were 78.8, 56.3 and 11.3%, respectively.

Much lower mortality rates have recently been reported. L. F. Meyer[75] has found that the use of sulfonamide drugs has decreased the mortality rate in Tel-Aviv from 50% before 1940 to 7% in recent years. During 1944 and 1945, Weihl, Rapoport and Dodd[106] treated 292 infants and children with acute diarrhea. The therapeutic regime consisted of continuous intravenous infusion of saline, glucose, plasma, blood, and sodium bicarbonate if the carbon-dioxide combining power was less than 30 vols. %. Sulfonamides were also administered and feedings were gradually initiated in accordance with the status of the patients. The patients' illness ranged from "mild" to "very severe"; about 40% fell into the group of "severely ill" and "very severely ill". Of the 292 patients, 22 (7.5%) died. Of these patients, 3 died within 3 hours after admission before adequate therapy had been instituted. Three other patients died of other causes after the diarrhea subsided. If these 6 patients are excluded, the mortality was 16 of 286 patients (5.6%).

It is apparent from the considerations and the data which we have presented that, without considering for the moment the therapeutic use of potassium salts, the mortality rate in infantile diarrhea is dependent upon a number of factors. These are the state of dehydration and general condition of the infant upon admission, the presence, development and control of parenteral infection, the adequate parenteral administration of saline, glucose, blood, and lactate or bicarbonate and the judicious initiation and regulation of oral feeding. The available literature[12,54,75,94,97,106] indicates that the general rate of mortality may be about 20%, but that in certain hospitals, the rate may fall below 10%, and, as in the case of Weihl's report, as low as 5.6%.

In view of the considerations just presented, the therapeutic use of potassium chloride by Govan and Darrow[42] can now be evaluated more precisely. During the months of June, July and August, a control group of babies with diarrhea was treated at the Harriet Lane Home in Baltimore by the conventional methods. Only those babies were admitted who were severely ill and who, it was thought, would not recover unless they received hospital treatment. There were 59 babies in this control group but in 6 of these, death was associated with sepsis or prematurity; in this group there were 17 other deaths. The corrected mortality in this control group which did not receive potassium was 17 of 53 (32%). During the months of September to November, 52 cases received, as previously described, fluids and feedings containing potassium chloride. It was believed that the patients in this group had, in general, the same distribution of severity of ill-

ness as the control group. Of these 52 patients, there were 5 deaths. One death was associated with sepsis and another with prematurity. The corrected mortality was, therefore, 3 out of 50 (6%). On the basis that the control and potassium-treated groups were strictly comparable, the difference between the mortality rates of the 2 groups is highly significant and attests to the efficacy of the potassium therapy.

Butler and his associates[11,90] have recommended the therapeutic use of a solution which contains 2.24 gm. of sodium lactate, 0.58 gm. of sodium chloride, 0.89 gm. of potassium chloride and 0.25 gm. of potassium monohydrogen phosphate per liter of 10% dextrose. In terms of m.Eq. the concentrations per liter, are as follows: sodium, 30 m.Eq.; chloride, 22 m.Eq.; potassium, 15 m.Eq.; phosphate, 3 m.Eq. Forty infants with persistent infectious diarrhea were given about 150 to 200 cc. of this solution per kg. of body weight per day together with 50 to 100 cc. of saline; frequent transfusions of plasma and blood were also administered. None of these 40 infants died. It will be noted that the solution recommended by Butler was much more hypotonic with respect to sodium and chloride ions than that recommended by Darrow which contained 122 m.Eq. and 104 m.Eq. per liter of these 2 ions, respectively.

Treatment of Potassium Deficiency in the Postacidotic Phase of Diabetes. When Holler[52] surmised that the respiratory paralysis which he was observing in a diabetic during the postacidotic phase of treatment might be due to a potassium deficiency, he drew blood for determination of serum potassium, then injected 1.5 gm. of potassium chloride in a 2% solution during the course of 35 minutes. The serum before treatment was subsequently found to have a potassium concentration of 2.5 m.Eq. per liter. Within 20 minutes after the end of injection, the patient showed dramatic improvement, and her respirations became normal. Additional potassium chloride was administered subcutaneously and orally during the next 2 hours to prevent recurrence of respiratory distress; the total amount given was equivalent to 8.7 gm. of potassium chloride. The patient experienced no further difficulty during her stay in the hospital. Her serum potassium and her electrocardiographic pattern were restored to normal.

Although there have been no reports concerning potassium therapy in large groups of patients in the postacidotic phase of diabetes, there have appeared a number of case studies, similar to that reported by Holler[52], which demonstrate rather convincingly that such therapy has been effective in counteracting the symptoms of potassium deficiency and averting the possibility of a fatal outcome. Such are the cases reported by Nicholson and Branning[82], Frenkel and co-workers[35], and Tuynman and Wilhelm[104]. Howard and Carey[53] have stated that potassium therapy in this condition is characterized, not only by the prevention of potassium deficiencies, but also by the absence of edema and hypoproteinemia and a quicker recovery to fitness and regulation by insulin.

The following doses and modes of administration have been found effective in relieving acute potassium deficiency of the postacidotic phase of diabetes: intravenous injection of 1.5 gm. of potassium chloride in a 2% solution during 35 minutes, followed by a subcutaneous infusion of a 200 cc. of a 2% solution of potassium chloride in 2 hours, and oral ingestion of 4 gm. of potassium citrate[52]; 0.6 gm. of potassium chloride by mouth every half hour until 3.6 gm. had been given[82]; 4 gm. of potassium chloride,

divided into 2 equal doses, by mouth[35]; 0.3 gm. potassium chloride by mouth at ½ hour intervals for 6 doses[104].

We may see, then, that in general, between 2 and 4 gm. of potassium chloride have been found effective. This corresponds to between 30 to 60 m.Eq. of potassium. It will be recalled, however, that the loss of potassium during the development of diabetic acidosis and treatment by saline-glucose solutions may be as much as 300 to 400 m.Eq. It follows, then, that where the diabetic acidosis has been very severe or prolonged, as in Holler's case, larger doses, up to about 8 or 10 gm. (100 to 125 m.Eq.) of potassium chloride may be used during the first day of therapy, and may be continued if the symptoms of hypopotassemia do not abate. In administering such solutions parenterally it is necessary, in this as well as in other conditions, to regulate the rate of introduction so as to avoid toxic levels of potassium ion in the serum. Howard and Carey[53] suggest that the serum reaching the heart must not contain more than 7 m.Eq. potassium per liter. This will usually be accomplished if solutions containing between 40 to 90 m.Eq. (1 to 2 gm.) per liter are infused at rates ranging between 8 and 12 cc. (120 to 180 drops) per minute. The problem of potassium toxicity will be discussed more fully later.

Treatment of Potassium Deficiency in Familial Periodic Paralysis. We have seen that the hypopotassemia in this condition is not due to an intracellular potassium deficiency, but rather to some factor which causes a shift of potassium from the extracellular to the intracellular compartment. There have been no systematic studies to determine the minimal amount of potassium necessary to counteract the hypopotassemia. In general, substantial but non-toxic amounts of potassium chloride or citrate have been given and found effective. Thus Herrington[51] treated 2 cases by administering orally 5 gm. of potassium citrate whenever prodromal symptoms of muscle weakness and soreness became evident. Pudenz and his associates[86] noted that the administration of 5 to 10 gm. of an aqueous solution of potassium chloride counteracted paralytic symptoms within 30 minutes to 1 hour and enabled the patient to walk 2 hours after administration. The concentration of serum potassium rose from 10 mg. to 24 mg. per 100 cc. (2.5 to 6 m.Eq. per liter).

Oral administration of 2 to 10 gm. of potassium chloride is adequate in most instances in abolishing episodes of paralysis and in preventing seizures[89]. However, there are some situations in which parenteral administration is necessary. For example, the patient reported by Pudenz and his associates[86] suffered a paralytic attack in which he became unconscious and required artificial respiration. The intravenous injection of 1 gm. of potassium chloride produced a striking improvement within 20 minutes; the patient sat up and was able to converse.

Postoperative Potassium Deficiency. A number of observations have recently been made to the effect that hypopotassemia may develop postoperatively in patients who are given only saline, glucose and amino acids[53,64,66,83]. An idea of the therapeutic procedure in this condition may be gathered from the recent work of Howard and Carey[53]. A chronically ill patient was found, 17 days after operation, to be extremely asthenic, with shallow respirations and barely obtainable peripheral reflexes. The serum potassium was 1.8 m.Eq. per liter. Amounts of potassium ranging from 54 to 134 m.Eq. (4 to 10 gm. of potassium chloride) per day were given for the next 8 days. The concentration of potassium in the serum rose slowly

until it attained a value of 3.2 m.Eq. per liter on the seventh day of therapy when there was a dramatic improvement in the clinical condition of the patient; he felt stronger, appeared more alert and the reflexes were now readily elicited. Two days later the serum potassium had risen to 4.1 m.Eq. per liter and the electrolyte pattern of the serum had been restored to normal. In this case a total of 991 m.Eq. of potassium (75 gm. of potassium chloride) had been administered.

Potassium Toxicity. A knowledge of the circumstances under which potassium may become toxic is necessary in order to withhold its administration when contraindicated or to avoid overdosage when such administration may ordinarily be employed. The reader will recall the electrocardiographic results which Winkler, Hoff and Smith[110] obtained upon infusion of isotonic (1.12%) potassium chloride into dogs. Cardiac arrest and death occurred at a serum potassium concentration of 14 to 16 m.Eq. per liter. This range of concentrations was obtained when the solution of potassium chloride was infused at a rate of 0.4— 0.8 cc. per min. per kg. for about 40 minutes and when a total of 0.2 to 0.3 gm. of KCl (3 to 4 m.Eq.) per kg. had been given. A much smaller amount, 0.05 gm. or 0.7 m.Eq. per kg. produces death if it is introduced rapidly enough so that a serum concentration of about 15 m.Eq. per liter is produced. On the other hand, Winkler and Smith[112] showed that when doses of 0.2 to 0.3 gm. (3 to 4 m.Eq.) of potassium chloride were infused into dogs at a sufficiently slow rate, the concentration of potassium in the serum rose only about 2 to 3 m.Eq. and no grave symptoms ensued. Calculation from this rise and the excretion of potassium indicated that considerable amounts had been deposited intracellularly.

It would appear from these experiments that the determining factor in toxicity and death as a result of administration of potassium salts is the concentration of potassium ion in the plasma and extracellular fluid. A rapid injection of a small amount can prove fatal whereas a slow injection or the ingestion of a large amount can be innocuous. The question arises whether these relationships also obtain in man.

Large amounts of potassium salts can be taken by mouth with the production of only minor toxic symptoms. Talbott and Schwab[100] record the ingestion of 30 to 36 gm. of potassium chloride daily in 3 equal doses without any apparent ill-effects. Keith and his co-workers[58,59,60] showed that the ingestion of potassium chloride or bicarbonate by normal individuals in doses ranging from 9.5 to 17.5 gm. (126 to 172 m.Eq.) led to paresthesias of the hands and feet, and increases in the amplitude of the T wave. The concentration of potassium in the serum rose from a normal value of about 16 to 20 mg. per 100 cc. to a level of about 30 mg. per 100 cc. or 7.5 m.Eq. per liter. The ingestion of smaller doses, 5 gm. of potassium bicarbonate (50 m.Eq.) by normal individuals, did not lead to any paresthesias, to only slightly detectible changes in the electrocardiogram and to only small increases in the concentrations of potassium. The increases were about 2 to 4 mg. per 100 cc. or 0.5 to 1.0 m.Eq. per liter.

It has already been pointed out that on the basis of experimental work in dogs, the lethality of potassium appears to be dependent on the concentration of the serum potassium; this fatal level in normal dogs is about 15 m.Eq. per liter or 60 mg. per 100 cc. It is obviously difficult to obtain comparable data in normal man. In the course of treating an infant with diarrhea by the subcutaneous in-

jection of a solution containing potassium chloride, Govan and Weiseth[43] observed the development of potassium toxicity. The infant survived although a level of 12.3 m.Eq. per liter (49 mg. per 100 cc.) of potassium was attained. Howard and Carey[53] record an experience in which a considerable amount of a solution of potassium salt was injected within a few minutes into a patient who clearly had hypopotassemia. Although no determination for serum potassium was done, the cardioscope showed an abrupt change from a low to a high potassium pattern. The patient died before the injection could be stopped. This case illustrates the necessity for introducing potassium salts parenterally at such a rate as not to exceed a concentration in the serum which is toxic to the heart.

It has been possible to obtain a more precise idea of the toxicity of potassium in patients with renal impairment. The following data show that the lethal level of serum potassium in such patients is about 10 m.Eq. per liter. Marchand and Finch[71] reported 2 cases of spontaneous potassium intoxication in patients with uremia; no potassium other than that in the food or in blood transfusions had been given. It was possible to follow the electrocardiographic changes and the concentrations of potassium in the period immediately preceding death. In one patient in whom the N.P.N. had ranged from 155 to 208 mg. per 100 cc., the concentration of potassium was 9.2 m.Eq per liter 20 minutes before death and 9.8 mEq. per liter in blood taken from the heart immediately after death. In a second patient with an N.P.N. of 258 mg. per 100 cc., the concentration of potassium was 9.2 m.Eq. per liter 3 and ¾ hours before death and 10.1 m.Eq. at death. Stewart, Shephard and Horger[98] also reported an instance of spontaneous development of potassium intoxication and death in the course of the nephrotic stage of subacute glomerulonephritis; the concentration of potassium was 10.6 m.Eq. per liter at the time that the electrocardiogram showed auricular standstill and intraventricular block. It will be shown presently that in some studies in which potassium salts were fed to patients with renal impairment, serum potassium levels approaching those just recorded were obtained without the accompanying development of grave toxicity.

It may be of interest at this point to describe the clinical symptoms of hyperpotassemia and potassium toxicity. We have already noted the cardiac findings, particularly as evidenced in the electrocardiogram. Keith and his co-workers[59] observed that paresthesias of the extremities developed when the concentration of the potassium in the serum approximated 7.5 m.Eq. per liter. This held for normal individuals as well as those with renal insufficiency. Finch, Sawyer and Flynn[30] found that flaccid paralysis may also be present at higher, near-lethal levels of potassium in the serum. Such paralysis may involve the extremities and, to a lesser degree, the trunk.

The susceptibility of patients with renal impairment to hyperpotassemia and potassium toxicity is, quite obviously, due to decreased excretion of potassium. However, such patients may have a tissue potassium deficiency. It is of considerable importance from a therapeutic point of view, to know to what extent they may receive potassium. Greene and his associates[45] found that the ingestion of 19 mg. of potassium chloride (0.26 m.Eq.) per lb. of body weight by a patient with chronic glomerular nephritis increased the concentration of serum potassium to 44 mg. per 100 cc. (11 m.Eq. per liter); no statement was made concerning the development of toxicity.

This observation is not in agreement with those of Marchand and Finch[71] and of Stewart, Shepard and Horger[98] which indicate that 10 m.Eq. per liter is a lethal level. Winkler and his co-workers[111] administered oral doses of potassium ranging from 67 to 134 m.Eq. (5 to 10 gm. of KCl) to 5 patients with renal impairment. The concentrations of serum potassium increased in each of these patients; the maximal levels ranged from 6.3 to 8.0 m.Eq. per liter. Although similar doses did not produce any higher levels of serum potassium in normal individuals, the decrease to pre-ingestion levels was much more delayed in the nephritic than in the normal. No symptoms of toxicity attributable to potassium were observed by Winkler and his associates in the patients with renal impairment.

Keith and Osterberg[59] have, however, obtained some toxic effects with somewhat smaller doses of orally administered potassium. Ten patients with severe renal insufficiency received 5 gm. of potassium bicarbonate (50 m.Eq. of potassium). One of these patients had a blood urea of 74 mg. per 100 cc. In 9 of these patients, the concentrations of potassium before ingestion of potassium bicarbonate ranged from 21.9 to 28.4 mg. per 100 cc. (5.6 to 7.3 m.Eq. per liter). One and a half hours after ingestion, the concentrations in these patients had increased in each case and ranged from 23.1 to 37.1 mg. per 100 cc. (6.0 to 9.5 m.Eq. per liter). Paresthesias of the extremities occurred in 4 of the patients; the serum potassium in these instances ranged from 31.1 to 35.8 mg. per 100 cc. (8.0 to 9.2 m.Eq. per liter). In the 6 patients in whom paresthesias did not develop, the serum potassium ingestion ranged from 19.9 to 37.1 mg. per 100 cc. (5.1 to 9.5 m.Eq. per liter). Electrocardiographic studies of these patients showed a definite toxic effect on the heart, namely, intraventricular block, in only 1 case; the concentration of serum potassium in this patient was 37.1 mg. per 100 cc. (9.5 m.Eq. per liter).

The studies which we have reviewed would indicate that the administration of potassium to patients with renal insufficiency should be a very guarded procedure. Although potassium intoxication may occur spontaneously, the work of Keith and Osterberg[59,60], of Greene[45], and of Winkler[111] indicates that small amounts of potassium, about 50 m.Eq. (3.7 gm. of KCl) may be given by mouth without serious danger to some patients with renal insufficiency. Although, therefore, the administration of potassium with renal damage is in general contraindicated, it would seem that when there is real evidence of potassium deficiency in such a patient, the cautious administration, under proper clinical supervision and with proper laboratory guides, of small amounts of potassium by mouth is to be considered. Even the intravenous infusion at very slow rates is not out of the question. However, this field of therapy will be greatly aided by further investigations concerning the tolerance to, and cellular storage of potassium in patients with renal insufficiency.

Ammonium Chloride. Ammonium chloride has a number of therapeutic uses. It is, however, with its application in the treatment of alkalosis that we are here particularly concerned.

Acidifying Action of Ammonium Chloride. The production of acidosis in man by ammonium chloride was first demonstrated by Haldane[47]. After ingesting amounts ranging from 5 to 55 gm., either in one or several doses, Haldane observed that this compound decreased the alveolar carbon dioxide pressure and the carbon dioxide capacity of the blood. Respiration increased in depth and frequency and, in one experiment, the volume breathed per

minute at rest increased 70%. Simultaneously, the urinary excretion of titratable acid and ammonia rose. Haldane assumed, although he did not demonstrate, that the formation of urea was increased. This, however, has been observed by subsequent investigators. The acidifying action of ammonium chloride has been confirmed by many investigators and the mechanisms of the body's reaction to the ingestion of this compound and other acid substances has been studied in great detail[31,36,39,56,63,69,93].

Haldane postulated that the ammonium chloride was metabolized to urea and hydrochloric acid according to the following reaction:

$$2NH_4Cl + CO_2 \longrightarrow CO(NH_2)_2 + H_2O + 2HCl$$

This may be regarded as an overall reaction. It has been established that the liver is the physiologically important site of the conversion of ammonia into urea[84]. The way in which ammonia is incorporated in the course of metabolic processes to form arginine, the immediate precursor of urea, has been considered in great detail by Krebs and Henseleit[62], Cohen and Hayano[14], Borsook and Dubnoff[6], and, most recently by Ratner and Pappas[89]. It may be expected that parenterally administered ammonium chloride will have essentially the same metabolic fate. In the course of a study of the intravenous injection of hypertonic solutions of various chlorides, Whelan[107] found that 0.1 gm. ammonium chloride per kg. of body weight could be injected per minute without toxic effect. This dose caused a decrease in the pH of the urine and an increase in the excretion of urea.

The effect of the introduction of ammonium chloride into the body on the acid-base regulating mechanisms may be described briefly. The alveolar ventilation is increased and, accordingly, the alveolar carbon dioxide pressure is decreased. For example, in a subject studied by Sartorius, Roemmelt and Pitts[93], the alveolar pressure decreased from a normal level of 41.0 mm. Hg. to one of 23.9 mm. after the ingestion of 40 gm. of ammonium chloride over a period of 3 days. This was indicative of an increase of 70% in alveolar ventilation. Gamble and his co-workers[37,39] showed that, in response to continued administration of ammonium chloride, there is first an increase in titratable acid and fixed base but that later, ammonia is substituted in progressively increasing amounts for fixed base in the urine. Pitts and his associates[93] have recently studied the relationship of electrolyte pattern to renal function in ammonium chloride acidosis produced by feeding 10 to 15 gm. over a period of several days. They observed that the plasma bicarbonate fell in exact proportion to the increase in plasma chloride. Since the load of bicarbonate presented to the tubules was decreased, the reabsorption of chloride increased. However, this increase was not large enough to prevent a net loss of chloride in the urine. Early in acidosis, the excess urinary chloride was neutralized mostly by sodium from the body buffers. The loss of sodium was reflected in a decrease of the concentration of sodium in the plasma. The loss of water from the body was derived chiefly from the extracellular fluid compartment. Of particular interest were the findings obtained within 2 hours after the ingestion of 10 gm. of ammonium chloride. The excretion of ammonia, as well as that of titratable acid, increased.

Treatment of Alkalosis. Bothe[7] appears to have been the first to use ammonium chloride by mouth in the treatment of alkalosis occurring either preoperatively or postoperatively. However, no specific doses were mentioned. Chalmers[13] treated 2 cases of alkalosis due to severe intestinal

obstruction from abdominal tuberculosis by administering per rectum 12 gm. of ammonium chloride dissolved in 5 to 6 ounces of water.

The use of parenteral ammonium chloride therapy for treatment of alkalosis was initiated by Zintel, Rhoads and Ravdin[113]. They found that the decrease in the serum carbon dioxide in a 150 lb. adult ranged from 0.6 to 1.5 and averaged 1.1 vols. % per gm. of ammonium chloride injected intravenously. Accordingly, they recommended a dose of 16 mg. per kg. of body weight in order to reduce the serum carbon dioxide content by 1 vol. %. Two % solutions of ammonium chloride in water, glucose or saline were employed. For example, in one patient with chronic peptic ulcer and stenosis, the infusion of 700 cc. of a 2% solution decreased the carbon dioxide content from 113 to 85 vols. %.

The effect of parenteral administration of ammonium chloride in the treatment of alkalosis of congenital hypertrophic pyloric stenosis in infants has been demonstrated by Forbes and Erganian[33]. The previous treatment of this condition consisted in parenteral administration of dextrose and saline or lactate-Ringer. It was thought that if sufficient water and electrolyte were given, a satisfactory correction of the alkalosis would be attained through renal activity. However, such an adjustment usually required 1 to 2 days and might not be accomplished in cases of very severe alkalosis. Indeed Forbes and Erganian refer to the occurrence of death in several infants before they could be prepared for operation.

Restoration toward a normal electrolyte pattern and acid-base equilibrium was achieved much more rapidly by the intravenous infusion of a 1/6th molar solution of ammonium chloride (8.9 gm. per liter) in isotonic saline or Ringer's solution. The doses ranged from 10 to 37 cc. per kg. of body weight and were administered during the course of 30 minutes. Maximal decreases in the carbon dioxide content and pH, and the maximal rise in the concentration of chloride were attained within 1 to 3 hours after the end of the infusion. For example, a severely alkalotic infant weighing 2.2 kg. was given 60 cc. of the ammonium chloride solution. The CO_2 content decreased from an initial value of about 105 vols. % to about 68 vols. % at the end of 2 hours. The pH fell from 7.63 to 7.47 and the chloride increased from 73 to 94 m. Eq. per liter.

The extent to which the normal electrolyte pattern and the acid-base balance is restored depends on the severity of the initial alkalosis and the dose of ammonium chloride. However, only a very general rule can be given concerning the relationship between the two. Upon theoretical grounds, it may be calculated that 1 cc. of a 1/6th molar solution of ammonium chloride should neutralize an equivalent amount of bicarbonate and reduce the carbon dioxide content by 22.4/6, or 3.7 cc. per liter of serum. If it is assumed that ammonium chloride and the bicarbonate are distributed in the total body water, then 1 cc. of ammonium chloride solution per kg. of body weight should reduce the carbon dioxide content by 3.7 x 3/2 or 5.6 cc. CO_2 per liter of serum or 0.56 vols. %. Actually, in the series studied by Forbes and Erganian, the lowering of the serum carbon dioxide content ranged from 0.33 to 1.77 and averaged 0.88 vols. % for every cc. of molar-sixth ammonium chloride solution administered per kg. of body weight. The cause for this variability requires further investigation.

Grace and Barr[44] studied a series of patients with intestinal obstruction in whom alkalosis had been precipitated by a combination of frequent gastric lavage and the administration of large

amounts of sodium lactate in conjunction with the use of sulfadiazine. Acute delirium was present in most of these cases. It was found that the intravenous infusion of a liter of a 2% solution of ammonium chloride during a period of 2½ to 3 hours resulted in an immediate improvement of the patient and elimination of the disturbing symptoms.

Toxic Effects of Ammonium Chloride Administration. Rizvi and Lucknow[92] used rapid injections of 10 cc. of a 5% solution of ammonium chloride to produce convulsion in schizophrenic patients. Such administrations correspond to a dose of about 7 mg. per kg. This dose is much less than the total doses, 89 to 330 mg. per kg., employed by Forbes and Erganian. However, these latter doses were usually infused very slowly during 30 minutes. Indeed, in one case, when a dose of 30 cc. per kg. of 1/6th molar ammonium chloride was given in 18 minutes, an interval shorter than the usual 30 minutes, toxic symptoms developed; the baby became pale, had twitchings of the eyelids and hands, breathed irregularly, developed bradycardia and showed a poor response to painful stimuli. It would, therefore, appear that the rate at which ammonium chloride is administered must be watched carefully in order to avoid toxic reactions.

In conclusion, it may be noted that potassium salts and ammonium chloride have gained an important place during the past few years in the armamentarium of parenteral fluid therapy. The judicious use of these substances has in many instances ameliorated the condition of the patient or even proven a life-saving measure. Basic studies of electrolyte and water balance and of renal function have done much to supply a rational basis for the use of these substances, but further investigations of this kind are indicated to increase and broaden their therapeutic effectiveness.

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RADIOLOGY

UNDER THE CHARGE OF

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ELECTROKYMOGRAPHY

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IN the application of roentgen methods to the investigation of clinical problems, radiologists and their colleagues have been principally concerned with the development of procedures which demonstrate changes in anatomical structure. Relatively few efforts have been directed toward the development of methods which detect physiologic disturbance. It is perhaps not surprising that radiology has followed this pattern in its early stages of growth. The evolution of roentgen engineering has been such that radiologists have been largely limited to methods in which one or more independently exposed films are made of the structure under examination. Although by proper timing of these exposures an evaluation of some functional processes may be attempted, such methods patently favor the visualization of anatomical structure rather than physiologic pattern.

Over the past few years, a number of developments have occurred which may well alter the trend which has heretofore existed. New techniques in angiocardiography have opened the door to the study of many problems in cardiovascular physiology. The recent application of Schmidt optics to the field of photofluorography may soon make possible motion pictures of a quality that compares favorably with conventional roentgenograms. Also, the roentgenoscope, which inherently would be an excellent physiologic tool if it were not for its poor rendition of detail, may soon have its deficiencies corrected if current research to intensify or brighten the fluoroscopic screen is successful.

In addition to the foregoing there has been one other instrumental development which appears to have considerable potential value in the study of physiologic phenomena. This is the electrokymograph[15], a device primarily developed for the recording of cardiac motion, but an instrument that may also be used to study the motion of any structure that can be seen roentgenoscopically or to study minute

changes in tissue density which may occur from physiologic activity.

The electrokymograph fundamentally consists of a small roentgen radiation detector, a simple amplifier, an oscillograph and a well regulated power supply. The radiation detector consists of a multiplier phototube and a small fluorescent screen, placed directly over the phototube's sensitive surface. The detector is attached to the frame of a conventional roentgenoscope and is mounted so that it assumes a position between the patient and the roentgenoscopic screen.

In the recording of cardiac motion with the instrument, the radiation detector is first centered roentgenoscopically over the border of the cardiac silhouette and then with the roentgen beam still turned on, the recording oscillograph is set in motion. As the cardiac border moves to and fro, the heart shadow may be seen to cover an increasing amount of the detector's fluorescent screen during the expansile phase of the cardiac cycle and a decreasing amount of the screen during the contractile phase. The intensity or brightness of the Roentgen rays passing through the detector's fluorescent screen thus varies in accordance with the motion of the heart border. Now these rays cause the emission of fluorescent light from the screen in proportion to their intensity and the underlying phototube reacts to this light by generating an electric current in proportion to the intensity or brightness of the fluorescent light. Therefore, the recording oscillograph to which the phototube is connected prints a wave whose amplitude is a function of the motion of the cardiac border under study.

In their original work with the electrokymograph, Henny and Boone[15,16] thought it important that the instrument's radiation detector be always centered with its long axis parallel to the structural motion being recorded. Subsequent experimental and theoretical investigations have proven this restriction to be unnecessary, however, and accordingly the mechanical design of the instrument has been simplified.

It may be of interest to the reader at this time to relate a few of the events that led to the early research in electrokymography. Jacobi, Janker and Schmitz[20] had conceived the idea of using an electronic radiation detector to record cardiac motion during the early 1930s. At that time the only roentgen device with which cardiac motion might be recorded was the roentgen kymograph, an instrument first proposed by Sabat[31] and later perfected by Stumpf[38]. This device, then as now, consisted of a lead diaphragm in which was cut a series of narrow transverse slits approximately one half inch apart. This diaphragm was placed in front of a roentgenographic film and during the exposure of a patient's chest, the film moved slowly downward behind the diaphragm. Any motion of the structures in the chest was recorded therefore on the film. Although much good work has been accomplished by this device[1,12,17,18,21,32,33,34,35], the analytic difficulties inherent in the unsharpness, the smallness and the brevity of its recorded waves have prevented it from becoming a widely used tool either in general radiology or in the study of physiologic processes.

As a means of overcoming the limitations of the roentgen kymograph, first Jacobi and his co-workers[20] and later Heckmann[14] considered the development of an instrument in which an ionization chamber served as a radiation detector. Unfortunately, within the limits of practical design it was not possible to build an instrument of this type which was both stable in operation and faithful in its recording char-

acteristics. Accordingly their efforts were not too successful. Early in 1940 however, the present writer[23] had begun to use multiplier phototubes in Roentgen-ray exposure control apparatus and it appeared that the characteristics of this device were such that it might serve as an excellent radiation detector for recording cardiac motion. The pressure of war activity prevented anyone from taking advantage of this development until arrangements were made with the U. S. Public Health Service early in 1945 to have Boone assigned to the laboratory of Chamberlain and Henny. Boone went to Philadelphia and work on the electrokymographic project was begun.

When the first instrument was constructed, there immediately arose the question concerning what name should be applied to the device. In correspondence and conference between Henny, Boone, Chamberlain and the author, several names were proposed including the term, fluorocardiograph. This name was discarded since the instrument was potentially useful in other fields than cardiography. The author suggested the term, electrokymograph, and although this name had several shortcomings, it was finally adopted by the group. Possibly the term, fluorokymograph, would have been better. However, the instrument has found use as a plethysmograph[9] in which visible light instead of roentgen radiation is used as the activating medium. In view of these and other considerations the name, electrokymograph, has persisted.

In addition to the pioneer work by Henny and Boone, fundamental electrokymographic research has more recently been conducteed by Hjelmare[19] in Sweden and Marchal[28] and Lian and Minot[23] in France. Hjelmare employs a Geiger-Muller counter as his radiation detector, whereas the French workers use conventional phototubes and sensitive amplifiers. Both groups have obtained good results. The simplicity of the multiplier phototubes employed by American investigators, however, favors the use of these devices over their European counterparts.

In their early work with the electrokymograph, Boone, Henny and their co-workers[2,3] devoted most of their effort to the analysis of cardiac motion and in particular to the motion of the left ventricle, the right auricle, the aorta and the pulmonary artery. For each of these structures they obtained complex, yet rather characteristic wave patterns. In order to correlate these wave phenomena with the events in the cardiac cycle that were responsible for them, it was necessary to record simultaneously with the electrokymographic tracings, a reference tracing of some other cardiac activity whose wave patterns were well understood. The carotid sphygmogram was used for this purpose.

Electrokymographic tracings were made by: 1, placing the patient in front of a roentgenoscope to which the instrument's radiation detector was attached. 2, guiding the radiation detector under roentgenoscopic control to a position over the heart border and, 3, then setting the oscillograph in motion. During the recording of the cardiac activity, the patient was requested to stop breathing.

The patients were examined in both the upright and recumbent positions. The sensitivity of the electrokymograph was adjusted individually for each patient so as to yield a tracing in which the amplitude of the waves approached 15 to 20 mm. With such an amplitude, the resolution of the various complex patterns was excellent and permitted ready analysis.

In this experimental work, the electrokymograph was arranged so that upward moving limbs of the recordings represented expansile or filling

phenomena of the heart while downward moving limbs represented contractile or emptying phenomena. The steeper the slope of a wave limb, the more rapid was the action or movement, and the less steep the slope, the slower was the action. Changes of slope upon a limb, in general, represented changes in speed of action and notches or serrations in the wave pattern represented smaller superimposed changes of action.

The wave forms for each of the 4 border areas of the heart and great vessels under investigation were found to be quite characteristic and to resemble closely the respective volumetric wave forms that are well known to physiologists. In spite of this basic resemblance to volumetric curves, however, certain differences were noted. It is believed that these differences are caused by factors which may be called "positional" in nature.

During ventricular systole and diastole, the heart undergoes a general movement because of its structure and relationship to the great vessels. Early in systole the long axis of the heart shortens as the base and apex move toward one another. At the same time the broad axis widens and the shape of the heart changes from an ellipsoidal to a globular configuration. This action frequently produces small outward movements of portions of the ventricular wall in early systole instead of the expected inward movement that would ordinarily occur when the volume of the heart is decreasing. In addition to the foregoing, 2 other positional changes have been described. One is caused by the pendulum motion which occurs when the aorta straightens; the second is a rotational motion which is caused by the spiral arrangement of the ventricular muscle bundles. During systole, this rotation causes cranial displacement of the apex, while in diastole the motion is reversed. These positional changes are of course superimposed on the volumetric changes and hence create a wave pattern of increased complexity. Sometimes they may be opposite in direction to the volumetric displacement and thus tend to counteract it; at other times they may be in phase with it and thereby produce an additive effect. It has been observed that these positional factors exert their influence principally during the early stages of systole and diastole.

The electrokymographic tracing of the left ventricular border has 2 major components, one descending, the other ascending. Each is preceded by a serration of variable amplitude and direction. The beginning of the serration that precedes the descending ejection phase of the cardiac cycle marks the onset of ventricular contraction and the raising of the intraventricular pressure to a sufficient level to close the mitral valve. As the contraction of the ventricular fibers continues the intraventricular pressure rises still further until the aortic valve opens. The time interval between the closure of the mitral valve and the opening of the aortic valve is called the isometric contraction phase of the heart cycle. Since there are no significant volumetric changes of the heart during this phase, the wave form of the electrokymographic tracing is entirely the result of positional changes of the heart. Also since the character of these positional changes varies widely from individual to individual and also from one region of the ventricle to another in the same individual, the wave form is quite variable. Usually however, the curve appears as a minor descending limb of gentle slope lasting for approximately 0.06 second.

When the aortic valve opens, blood is ejected rapidly into the aorta. During the early period ejection, positional factors of the heart continue to play a prominent role in determining the

ventricular wave form of the electrokymographic tracing. Frequently the ventricular wall exhibits a brief outward motion before its major inward motion occurs and hence the tracing may present a minor ascending limb of gentle upward slope before the major descending limb of ventricular ejection takes place. Toward the end of the ejection phase, the flow of blood into the aorta slows because of pressure equalization and the steep descending limb of the electrokymogram frequently tapers off.

At the end of ventricular systolic ejection, the phase of protodiastole, the first stage of diastole, occurs. This phase takes place just before the closure of the aortic valve and is usually marked on the electrokymogram by a minor upward serration, approximately 0.04 second in duration. However, as this wave form is principally the result of positional changes in the heart, it therefore varies from one individual to another to a considerable degree.

When the aortic valve closes, there follows a short interval before the mitral valve opens, called the isometric relaxation phase of the cardiac cycle. During this phase the ventricle is a closed chamber and therefore undergoes no volumetric change. Therefore here again, positional changes of the heart are the cause of any movement of the cardiac border. Usually this phase is marked on the tracing by a minor downward serration, approximately 0.10 second in length.

When the mitral valve opens there is an initial inrush of blood which carries the ventricular wall outward. This event is recorded electrokymographically as a major ascending limb of steep slope. This portion of the tracing marks what has been called the rapid diastolic filling phase of the cardiac cycle. It is followed by a phase in which the filling of the ventricle takes place at a slower rate and during which the electrokymogram continues to ascend but at a somewhat diminished slope. This phase, called the slowed diastolic filling phase, leads directly into the isometric contraction phase to begin again the cardiac cycle.

It will be evident from the foregoing that electrokymograms of the left ventricle constitute a powerful method for recording the mechanical events that take place within the heart. Electrokymograms of the pulmonary artery and the aorta also reveal with striking definition the phenomena associated with those structures. The electrokymogram of the pulmonary artery presents a wave form with a sharply rising limb, a rounded crest and a slowly descending limb. The sharply ascending limb marks the vigorous ejection phase of ventricular systole and begins at the opening of the pulmonary valve. The first part of the descending limb probably occurs during the late phase of ventricular systole. Some distance from the peak of this limb there is a brief notch which is related to the closure of the pulmonary valves.

The electrokymogram of the aorta is similar in many respects to that of the pulmonary artery. It frequently is asynchronous with the tracing of the pulmonary artery, however, and therefore may be differentiated from it. Its incisural notch also is very much less prominent than that of the pulmonary artery.

A truly characteristic electrokymogram for the right auricle has been extremely difficult to establish. This appears to be due to the fact that the right ventricle usually superimposes its motion upon it and thereby creates a wave pattern that is difficult to analyse. However, it has been found that with careful time measurements and cross correlations, the time of auricular systole can usually be identified. The lower the point chosen on the right

auricular border, the more prominent is the influence of the right ventricle and the greater is the difficulty in defining the auricular activity. Indeed in many cases that have been studied, a pure ventricular wave has been recorded on the heart border in the vicinity of the cardio-hepatic angle. Thus the right ventricle may frequently contribute to the right heart border in the antero-posterior silhouette.

Until now, our discussion has been concerned mainly with the application of electrokymography to the study of normal physiologic phenomena in the heart and great vessels. A review of the literature pertaining to its use in abnormal physiologic states therefore appears to be in order. However, before proceeding to this phase of the subject, it is worthwhile to direct attention first to a number of engineering problems that have been encountered in electrokymographic development. In general, these problems have had a somewhat limiting influence on the breadth of application of the instrument.

As we have seen, the wave forms presented in electrokymograms of the heart are quite complex. The faithfulness with which the tracings actually record cardiac movement therefore is dependent on the frequency response of the electrokymograph. If the instrument is able to record equally well all of the frequencies generated by the cardiac segment under investigation, then the tracing will constitute a precise record of cardiac motion. On the other hand, if one of the movements of the heart generates a wave form of let us say 20 cycles per second and the electrokymograph has a frequency response that extends only from 0 to 10 cycles per second, that particular movement of the heart will go unrecorded; hence the electrokymogram will not constitute a faithful record of the cardiac phenomena.

Now electrokymographs using multiplier phototubes and calcium tungstate fluorescent screens as their radiation detectors inherently are limited in their frequency response only by the design of their amplifier and oscillographic equipment. Indeed, if necessary, these components can easily be designed to provide a frequency response from 0 to several kilocycles. However, the characteristic of present-day roentgenoscopes make the use of such equipment quite impossible. Conventional roentgenoscopes are operated with raw AC or unfiltered rectified AC potentials and hence the intensity of the Roentgen rays generated by them rises and falls periodically at a frequency of 60 or 120 cycles per second. If means are not provided in the electrokymograph to attenuate sharply these frequencies, the tracings that result are essentially unreadable. Now, it is not possible to attenuate a particular frequency without causing some attenuation of frequencies in the nearby ranges. In fact, unless considerable care is taken, the frequency response of an electrokymograph which contains provision for filtering out the 60 or 120 cycle signal arising in the roentgenoscope, may also discriminate severely against frequencies as low as 2 or 3 cycles. Kay, Wood, Zinsser and Benjamin[22] measured the frequency response of one electrokymograph and found the response at 5 cycles per second 38% lower than at 1 cycle per second; at 20 cycles the response was down 87%. It is quite obvious that such an electrokymograph will be unable to record much of the finer detail that may exist in a cardiac activity.

Although the first electrokymographs exhibited poor frequency responses, it is fortunately possible to design instruments that have a flat response from zero to about 30 cycles and still effectively filter out the 60 or 120 cycle signal from the roentgenoscope. Hence-

torch, electrokymographs having such characteristics should be easily attainable and it will be interesting to follow the additional information that these instruments will provide. It may be worthwhile to explore the possibilities of an electrokymograph operated from a constant potential roentgenoscope. If the instrument is able to record over a truly wide frequency range, the resulting high resolution of the device may provide information far beyond our present limits.

Another engineering problem that has been encountered in electrokymography is the difficulty with which the amplitude of the recorded tracing can be correlated with the amplitude of the actual motion under investigation. When a thin patient is examined, the intensity of the roentgen radiation reaching the electrokymograph is high and hence a normal cardiac excursion will produce an abnormally large amplitude in the electrokymogram. Conversely when the patient is overweight the intensity of the roentgen radiation incident upon the electrokymograph will be low; under these conditions the same amount of cardiac motion will produce a tracing of low amplitude. This difficulty may be overcome to some extent by an adjustment of the sensitivity of the electrokymograph to meet the changing intensity of the radiation that exists from one patient to another. Unfortunately, however, it is extremely difficult to calibrate such a sensitivity control in a manner that will insure a quantitative relationship between the amplitude of the electrokymogram and the amplitude of the motion that produced it. On the surface the underlying causes of this difficulty may not be readily apparent. However, it must be remembered that the electrokymograph is an instrument that records changes in light intensity received from a Roentgen-ray fluorescent screen. A moving structure, such as the heart or one of the great vessels, therefore will generate a wave pattern on the instrument's oscillograph.

Now the heart and great vessels differ widely in their ability to absorb roentgen radiation. The heart, being a large structure, absorbs a large percentage of the radiation projected through it while the pulmonary artery, being of much smaller caliber, absorbs only a small percentage of the radiation incident upon it. Accordingly, a given movement of the heart will produce tracings of much greater amplitude than the same amount of motion in the pulmonary artery. This same phenomenon will also cause the production of electrokymograms of different amplitude in 2 patients with equal average Roentgen-ray transmission and equal cardiac motion, if in 1 patient, the heart is larger than in the other.

From the foregoing it appears that the solution to the problem of correlating movement amplitude with tracing amplitude is well night insurmountable. With this thought in mind, a number of workers have expressed the opinion that this problem in reality is of no great importance under most circumstances. They point out that the great amount of information provided by the high resolution of electrokymographic tracings permits one to resolve most problems to which the instrument is applied. They further state that if quantitative information on the amplitude of a given motion is desired, it may be easily obtained from a roentgen kymographic film. Although this reasoning is doubtless sound, it is hoped that efforts will be continued to find ways and means of solving the problem.

During the past few years, electrokymography has been used by an increasing number of workers in the study of normal and abnormal cardiac physiology. Characteristic patterns

have been established for myocardial infarction and aneurysm, constrictive pericarditis, tricuspid and mitral heart disease and a number of congenital anomalies. Chamberlain[6] first demonstrated the spectacular changes that occur in the ventricular electrokymogram taken in the region of a myocardial infarct. In this situation the major descending and ascending limbs of the tracing that normally occur during the ejection and diastolic filling phases are reversed; that is, in myocardial infarction, the descending and ascending limbs occur during the diastolic filling and ejection phases and hence present a paradoxical sequence. This finding has also been observed by Luisada and Fleischner[25]. Stauffer and Jorgens[37] also found a similar abnormality in 2 histories of ventricular aneurysm. These workers found that the most rapid outward movement of the aneurysmal wall occurred during the isometric contraction and early systolic ejection phases of the cardiac cycle. During the latter part of systole the wall remained relatively stationary, only to move sharply inward shortly after the closure of the aortic valve. They also interestingly observed that roentgen kymograms of these patients demonstrated the changes found in the electrokymograms only with the greatest difficulty.

Although paradoxical movement of the ventricular border in the great majority of instances probably indicates the presence of a myocardial infarct, Gillick[11] has observed a few instances of the phenomenon in normal healthy young adults. Gillick has explained the observation by postulating that the shortening of the interventricular septum during systole is greater than usual and that almost the entire decrease in the volume of the ventricular chambers is due to this septal hyperactivity. As a result the ventricular wall actually is displaced outward during systole. Whether or not this explanation is sound must await further observation.

Another instance where electrokymography appears to yield valuable information concerning the status of the myocardial muscle is in the relatively great precision with which it permits the measurement of the isometric relaxation phase of the cardiac cycle. Physiologists, including Wiggers[39] and Burstein[5], have believed for some time that this phase provides an excellent index of the relaxation process and of the functional condition of the myocardium. Unfortunately, clinical methods to measure the duration of this phase have not heretofore been available. Luisada, Romano and Torre[26] working with normal subjects and with patients with mitral stenosis, and Boone, Randak, Ellinger and Oppenheimer[4] working with normal and hypertensive individuals and with patients having myocardial infarction and bundle-branch block, appear not only to have strikingly confirmed the concepts of Wiggers and Burstein but also to have demonstrated that electrokymography is a simple and reliable method for measuring the duration of the phase. The observations of Boone and his group indicate that the duration of the isometric relaxation phase in the normal healthy adult ranges from 0.06 to 0.16 second with 71% of the observed cases falling between 0.10 to 0.13 second. The pathological group on the other hand exhibited isometric relaxation times ranging from 0.10 to 0.22 second, with 71% falling between 0.15 to 0.18 second.

The causes of increased duration of isometric relaxation have been the subject of considerable conjecture by physiologists. Three factors have been suggested to account for the phenomenon. These include: *a*, the inherent rate of muscular relaxation. *b*, the intraventricular pressure at the onset

of isometric relaxation, and *c*, the intra-atrial pressure at the end of isometric relaxation.

In hypertension Boone and his co-workers believe that the increased intraventricular pressure at the end of systole results in a greater pressure differential between the ventricle and auricle and hence a prolongation of the isometric relaxation phase. Later as the hypertrophy of the musculature progresses and its nutrition becomes impaired, the inherent rate of relaxation becomes slower. It was also found in 2 cases with congestive failure that the duration of the isometric relaxation phase returned to normal levels. It is believed that this reversion is caused by a decrease in the intraventricular pressure at the end of systole as compared to the compensated hypertensive state. Also the elevated intra-atrial pressure in the decompensated state probably terminates the phase prematurely by reducing the differential pressure between ventricle and auricle still further.

In cases of bundle-branch block and myocardial infarction it appears that the principal factor responsible for the prolongation of the isometric relaxation phase is an increase in the inherent rate of muscular relaxation following metabolic and structural changes in the ventricular muscle. Boone and his co-workers also speculated that the prolonged relaxation phase might be a compensatory measure to maintain adequate coronary blood flow since Gregg and Green[13] have demonstrated a large coronary blood volume flow during this phase of the cardiac cycle.

Some rather striking changes of the ventricular electrokymogram have been observed by Gillick and Reynolds[10] in cases of constrictive pericarditis. The ascending limb of the rapid diastolic filling phase commences in its normal fashion but, after completing a portion of its excursion, it ends abruptly in a sustained plateau which persists until the ejection phase of systole begins. Apparently the pericardium sharply restricts the outward motion of the ventricular wall soon after the ventricle has begun to fill. In a review of the electrokymograms presented by Stauffer and Jorgens[37] it is interesting to observe that their Case VI presents such a pattern at the left lower ventricular border and it therefore may be presumed that the primary diagnosis was a constrictive pericarditis rather than the tricuspid regurgitation that was reported. The other clinical findings in this case are also quite consistent with this disease.

Stauffer and Jorgens[37] also noted abnormalities of the aortic electrokymogram in patients with interatrial septal defects. A rather broad plateau at the height of the curve plus an unusually deep incisura were observed. Unfortunately these tracings were not published in their communication and it is therefore difficult to judge how striking the changes were. Stauffer and Jorgens explained their finding on the changed hemodynamics associated with the intracardiac shunt and transmitted motion from the adjacent enlarged pulmonary artery.

Luisada and Fleischner[27] have recently reported characteristic changes of the left auricular electrokymogram in 23 patients with lesions of the mitral valve. The normal electrokymogram of the left auricle as found by these workers consists of: 1, a sharp presystolic downward limb whose trough coincides with the closure of the mitral valve, 2, a serration of inconstant amplitude during systole, and 3, an ascending limb of variable slope during early diastolic collapse. In the cases with mitral regurgitation, this normal pattern was interrupted by a steep expansile wave at the beginning of ventricular systole which ended in a

broad plateau which persisted until the opening of the mitral valve. The wave then descended sharply at the beginning of ventricular diastole. The changes are the result of mitral regurgitation.

Interesting use of electrokymography in the study of asynchronism of the right and left ventricles has recently been reported by several workers[7,8,24]. Chamberlain and his co-workers made consecutive electrokymograms of the pulmonary artery and of the aortic arch with the carotid sphygmogram. The time interval between the onset of pulmonary ejection and the onset of aortic ejection was determined by using the carotid sphygmogram as a standard of reference. In normal subjects asynchronism of ejection occurred in 51 of 68 subjects. Left ventricular ejection led by 0.01 to 0.03 sec. in 32 cases; right ventricular ejection led by 0.01 to 0.03 sec. in 19 cases.

In patients with intraventricular block, the asynchronism was strikingly accentuated. In 6 patients with right bundle-branch block the onset of the ejection phase of the right ventricle lagged behind the left ventricle from 0.04 to 0.05 second. In 9 patients with left bundle-bunch block the left ventricular ejection lagged behind the ejection phase of the right ventricle from 0.04 to 0.07 second. In a tenth patient the difference was 0.03 second (the upper limit of normal).

The asynchronism which normally occurs between the right and left ventricles has been used by Gillick[11] to determine the source of the pulmonary blood supply in a case of unilateral pulmonic stenosis. He was able to demonstrate beautifully that on the normal side of the chest the pulmonary pulse waves were synchronous with those of the right ventricle, whereas on the stenotic side the pulsations were synchronous with those of the aorta. The blood supply to the lung on the stenotic side was therefore through bronchial collateral arteries. This case seems to indicate that electrokymography may be able to solve the difficult problem of ascertaining before surgery the pulmonary blood supply in patients with varying grades of pulmonic stenosis (*i.e.*, patients with such congenital anomalies as the tetralogy of Fallot).

Another physiologic investigation using electrokymography has recently been published by Kay, Wood, Zinsser and Benjamin[22]. These authors studied the validity of electrokymograms for measuring the diametric change of the aorta and pulmonary artery during circulatory disturbance. In their investigation, voluntary straining was employed as a test circulatory disturbance. It was found that qualitatively the changes in the amplitudes of the electrokymographic tracings paralleled coincident changes in pulse pressure in the brachial artery and that the amplitude of aortic pulsations, after correction for pulse rate, have a quantitative relationship to pulse pressure approximating that which would be expected between aortic diameter change and pulse pressure. More than a good approximation cannot be expected however since differences in the diameter of the aorta during and after straining cause the aorta to have different Roentgen-ray transmissions. Therefore, a given border movement of the aorta under the 2 conditions will produce electrokymograms of different amplitude.

Finally, what probably will prove one of the most important applications of electrokymography has just been proposed by Ring, Balaban and Oppenheimer[30]. These workers have conducted a study in which the amplitudes of the electrokymograms taken over the body of the left ventricle were correlated with the cardiac output, as determined by the ballistrocardiographic method of Starr[36] in 28 patients. A surprisingly good correlation

was found. It is rather unfortunate, however, that the ballistocardiographic method was employed as a standard of reference in this investigation as it is thought by many to be less reliable than the methods of Fick and Stewart. If further studies, using these latter methods of reference, demonstrate an equal or better correlation between cardiac output and the electrokymogram, a simple clinical procedure for determining this parameter will at last be at hand. Since ventricular electrokymograms resemble very closely the volumetric changes that occur in the heart, there is good reason to expect that an excellent correlation will be obtained.

From the material that has been reviewed in the foregoing paragraphs, it is evident that the electrokymograph is a radiologic tool of rapidly developing significance. With several other recent developments it is raising the curtain on a new era of roentgen investigation, an era of physiologic rather than anatomic study. It will be interesting to pursue the many new applications of electrokymography that doubtless will occur in the years to come. The method has certainly shown remarkable potentialities in the few years since its inception.

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BOOK REVIEWS AND NOTICES

THE FUNDAMENTALS OF PULMONARY TUBERCULOSIS AND ITS COMPLICATIONS. Edited by EDWARD W. HAYES, M.D., *et al.*, American College of Chest Physicians. Pp. 480; 74 ills. Springfield, Ill.: Charles C Thomas, 1949. Price, $9.50.

THIS book has been prepared by an editorial committee of the American College of Chest Physicians. Its purpose is to present in a concise manner fundamental information on the cause, prevention, diagnosis, treatment and control of tuberculosis. The committee calls attention to the diversity of material and sources with which medical students, practicing physicians and teachers should be familiar in order to obtain a working knowledge of tuberculosis, and has attempted to save them the effort of extensive search through the literature by bringing together in a single volume principal facts in the wide range of subject material covered. The result has been a successful presentation of the chief aspects of tuberculosis treatment and control, with emphasis on modern developments. The 26 chapters cover in commendable fashion basic knowledge in the fields of anatomy, bacteriology, immunology and pathology, physical, laboratory and Roentgen-ray diagnosis, treatment by sanatorium methods, psychosomatic aspects of the disease, bronchial tuberculosis, minor and major surgical procedures in the treatment of tuberculosis, public health aspects of its control, tuberculosis of special systems and various complications. A useful bibliography is appended. The book can be highly recommended as a ready reference for information in the various fields of tuberculosis. E. L.

A TEXTBOOK OF HISTOLOGY. By ALEXANDER A. MAXIMOW, Late Prof. of Anatomy, and WILLIAM BLOOM, Prof. of Anatomy, Univ. of Chicago. 5th ed. Pp. 700; 562 ills., 32 in color. Phila.: W. B. Saunders, 1948. Price, $8.50.

THIS 5th edition follows in its main outlines the plan of earlier editions. Recent advances have been incorporated without increasing the size of the book, and examples of the newer histochemical techniques have been judiciously chosen. Both features are in keeping with the general nature of the subject, allowing presentation of the more fundamental aspects of histology in a comprehensive and readable manner. The paper, type and illustrations are of unusual excellence.

C. B.

HINDU MEDICINE. By HENRY R. ZIMMER, Ph.D., Formerly Prof. of Sanskrit, Univ. of Heidelberg. Edited by LUDWIG EDELSTEIN, Ph.D. Pp. 201. Balt.: Johns Hopkins Press, 1948. Price, $4.00.

THIS is in no sense an account of Hindu medicine through the ages, or even through ancient times, nor is it intended to be one. It is, however, an interesting view of the high points of pre-Aryan, Vedic, Buddhistic, Tantric and Ayurvedic philosophy in relation to medical theories and practices closely correlated with the pervading myths and philosophy of Hinduism.

The 7th series of the Noguchi Lectureship on the History of Medicine was given by Professor Zimmer in 1940. Three years later he died before his revision of the material for publication had been completed. The first 2 of the 3 lectures are published substantially as they were found in his papers, even though fragmentary. To augment the analysis of Hindu medicine the editor has contributed a lengthy Preface outlining Zimmer's concept of Hindu culture, and has included, as an act of piety, as many as possible of the scattered notes and outlines for the missing chapters. A stimulating and valuable combination of Hindu medical lore, mysticism and philosophy emerges. E. K.

SKIN DISEASES IN GENERAL PRACTICE. By F. RAY BETTLEY, M.D., Middlesex Hospital, London. Pp. 260; 96 ills. London: Eyre & Spottiswoode, 1949. Price, 21 s.

HERE Bettley has undertaken to do what many dermatologists have wanted to do: write a book for the general practitioner covering only those diseases which are common and discussing them adequately enough to be practical. Although the author has done a yeoman's job, the selection of topics to be discussed will not meet the approval of all authorities, since determination of what is common will vary with the individual specialist as well as with the general practitioner because of differences in the composition of their practice. On the whole, however, in spite of the omission of some diseases,

others not uncommon but which pose difficult situations to the practitioner (*e.g.*, urticaria, erythema multiforme) are hardly mentioned. On the other hand, it might be desirable to omit detail on certain therapeutic procedures requiring special skill and training (*e.g.*, thorium-X).

This is one of the better handbooks recently published, and it merits wide consideration. H. B.

HUTCHISON'S FOOD AND THE PRINCIPLES OF DIETETICS. Revised by V. H. MOTTRAM, M.A. (Cant.), and GEORGE GRAHAM, M.D. (Cant.), F.R.C.P. (Lond.). 10th ed. Pp. 727. Balt.: Williams & Wilkins, 1948. Price, $6.75.

DIETETICS and nutrition are reverse sides of the same coin. This is a detailed survey of human foods and their composition which correlates this information with the current understanding of what happens to the separate components of food during digestion and endogenous metabolism. Emphasis is given to both psychologic influences and individual variation factors which most American textbooks tend to underestimate. This new tenth edition discusses much of the new data which has accumulated during—and largely because of—the war years. Like many English texts it is eminently readable.

I. W.

SYPHILIS: ITS COURSE AND MANAGEMENT. By EVAN W. THOMAS, M.D., Prof. of Clinical Medicine, New York Univ. College of Medicine. Pp. 317; 59 ills. New York: Macmillan, 1949. Price, $5.50.

ANY present-day exposition on the course and management of syphilis must be tentative and the author a person of great courage to be willing, as Dr. Mahoney hopes in the introduction to this volume, to "build a series of revisions which will carry the disease through the period of change and which will attempt a final evaluation of the events now taking place." As a seconder to this hope, the Reviewer believes Dr. Thomas has produced a concise review of the status of syphilis today and while he does not accept all the conclusions reached, he feels that this volume will at least fulfill the purpose of stimulating thought and further investigation, but because of the complicated mode of presentation, it is far from the mark of giving "busy individuals a practical understanding of the principles underlying the modern diagnosis and treatment of syphilis." For the Specialist, however, there is much to commend this book. While most of the data presented are interpreted personally by Dr. Thomas, he has sought assistance of many able authorities including Dr. Theodore Bauer, Dr. Charles R. Rein, Dr. Bernhard Dattner and Dr. Joseph Earle Moore.

The section on Interpretation of Quantitative Serologic Tests for Syphilis is probably the most detailed compilation the Reviewer is aware of. To counterbalance this worthy service there are many views which may be misleading to the less critical practitioner. For example: the experience of the Author regarding the location of mouth spirochetes only at the margin of the gums, thus discrediting the validity of darkfield results from specimens removed from other oral sites; his views on reinfection tend a little on the side of uncritical definition since his only absolute criterion of reinfection is the development of a new chancre at a different site from the original one (p. 39).

The Reviewer feels that some expansion of the text and attention to the loose ends produced by the present "shakedown cruise" will lead eventually to the production of one of the outstanding volumes on syphilis.

H. B.

CARDIOLOGY. By WILLIAM EVANS, M.D., Physician to the London Hospital. Pp. 310; 269 figs. New York: Paul B. Hoeber, 1948. Price, $7.50.

IN the preface Dr. Evans states that this book was written for medical students in preparation for higher examination and for busy practitioners. It was not intended to compete with standard text-books. The subject matter is large and the discussion is short. Physiological and pathological aspects of heart disease are considered briefly and many American electrocardiographic aspects of myocardial infarction are lacking. The roentgenographic coverage is excellent. I do not believe that this work is sufficiently detailed. The book is clearly written, is well printed and is excellently bound. H. F.

DISEASES OF THE LIVER, GALLBLADDER AND BILE DUCTS. By S. S. LICHTMAN, M.D., Ass't. Prof. of Clinical Medicine, Cornell Univ. Medical College. 2d ed. Pp. 1135; 147 ills., 4 in color. Phila.: Lea & Febiger, 1949. Price, $18.00.

THIS textbook is a comprehensive work dealing not only with the diseases, as its title suggests, but also with the anatomy and physiology of the liver and biliary structures. In addition it covers the modern techniques for the study of hepatic and biliary diseases. It has been effectively revised and the ma-

terial is presented in better order than in the original edition. An exhaustive number of references is available at the conclusion of each chapter.

The great amount of knowledge that has been accumulated during the past decade concerning hepatitis is strikingly demonstrated by comparing the brief discussion of the possible etiologies of catarrhal jaundice in the 1st edition with the 104 page chapter on viral hepatitis in this one. Liver function tests are covered in 2 ways: first, in a separate chapter concerned with their technical and physiological aspects; second, with their application to specific diseases.

The book will be of great value to anyone interested in liver disease from either the clinical or the investigative point of view.

W. S.

MEDICAL ETYMOLOGY. By O. H. PERRY PEPPER, M.D., Prof. of Medicine, Univ. of Pennsylvania. Pp. 263. Phila.: W. B. Saunders, 1949. Price, $5.50.

EVERY medico—student or M.D.—should be exposed to this novel work. Once past a necessarily repelling title, many more than the followers of semantics will soon find enough of interest or value to lead them to proceed further. The author's well-known combination of an excellent sense of proportion and practicality with a dexterity of presentation and lightness of touch is in welcome contrast to the usual medical text. Humor happily keeps breaking through (cp. the remarks on rigor, phrenic, prognosis, xerostomia, morgue, to mention but a few). One thinks, too, of his address at the dinner of the Association of American Physicians in 1948.

The *"Verb. sap."* of the book's motto is more apt to be sufficient after a deviously derived meaning has been explained in this book than it is to the linguist who has a correct translation of its components but a totally incorrect definition (Cp. epithelium). Nevertheless, the etymology of a scientific word usually gives a correct idea of its meaning and in any case affords a convenient peg of association to aid the memory burdened by a flood of new and forbidding terms. To digress a little further, the layman is wrong, though perhaps excusably so, when he accuses the doctor of professional pomposity when he resorts to polysyllables to express his meaning. Who would deny that it is easier for the physician to speak of, let us say, "choledochojejunostomy" instead of "the operation of making an opening between the bile duct and the empty part of the bowel?"

Dr. Pepper is over-modest in disclaiming originality and completeness of material. His approach is original and such a work could never be complete.

The less than 4000 terms are presented in some 15 and 20 categories, such as Anatomy, Psychiatry, Radiology, but all can be readily found with the help of the good index. One inevitably misses some words which could profitably have replaced others that have obvious meanings or derivations or are excessively rare or vary but little from words that have been included. Inevitably, also, one disagrees with some derivations or points of view, such as that on the use of eponyms; but at the same time one is impressed with the author's knowledge of words and their history, or, what amounts to the same thing, his ability to uncover and utilize such knowledge. We can hope that his continued interest will lead before long to another bigger and even better edition.

E. K.

HIPPOKRATES-FIBEL. Von Dr. med. RICHARD KAPFERER, München und Bad Wörishofen. Pp. 355. Stuttgart: Hippokrates-Verlag, Marquardt & Cie., 1949. Price, D.M. 16.50.

FROM his lengthy translation of the complete works of Hippocrates into modern German (1934-1940), Dr. Kapferer has selected for this Fibel, or Primer, several hundred passages that are calculated to throw light on the ways of thinking and the actual medical knowledge of the Hippocratic School. The extracts vary in length from a single line to a page or more, and are grouped under 69 headings such as the Oath; the Aphorisms; Diet; Airs, Waters, Places; Hemorrhoids.

For the not inconsiderable number who would like to know more about details of Hippocratic medicine but are unable, or think they are unable, to find the necessary time to search through the Hippocratic Corpus, such a book as this is better able than its parent to provide the half loaf that is proverbially better than none.

The volume has an interesting provenance. Published and copyrighted by Marquardt & Co., of Stuttgart in 1943, it was printed at Breda in Holland on war-paper (date not given), and reaches us for review in 1949.

E. K.

STUDIES ON HOOKWORM DISEASE IN SZECHWAN PROVINCE, WEST CHINA. By K. CHANG and Co-workers. The American Journal of Hygiene Monographic Series, No. 19, May, 1949. Pp. 152; 34 figs. Balt.: Johns Hopkins Press, 1949. Price, $3.00.

THE occurrence of hookwork disease in any population depends upon: 1, human infection; 2, soil pollution; 3, an environment favorable to the development of infective hookworm larvae in the soil, and 4, human contact with the infected soil adequate to continue the parasite in its host. In many parts of the world hookworm disease results from promiscuous defecation by people near their houses or in other often frequented sites. In China, however, hookworm infection is more of an occupational disease of the farming population. For in China human excrement is carefully conserved and used as fertilizer. It is not so much the use of human feces to fertilize crops that maintains the infection but the particular methods employed in planting, cultivation or harvesting. These methods may vary with the locality. Thus an understanding of the epidemiology and control of the parasite must come from a complete study of agricultural practices. In this monograph Dr. Chang and his associates have presented their studies of hookworm disease and its control in a large and important province of China. The book is well written, adequately illustrated and an interesting account of their work.

H. R.

ARTHRITIS AND ALLIED CONDITIONS. By the Late BERNARD I. COMROE, M.D. Edited by JOSEPH L. HOLLANDER, M.D., Univ. of Pennsylvania. 4th ed. Pp. 1108; 370 ills. Phila.: Lea & Febiger, 1949. Price, $16.00.

THIS edition of Comroe's book on arthritis has been completely revised and brought up to date by Dr. Hollander of the University of Pennsylvania Hospital. There are 17 contributors to this excellent book of over 1100 pages in which the illustrations and bibliography are well chosen and carefully screened.

There might be some criticism of Part X, for here the book departs from its chosen role as a treatise on arthritis and considers in detail such subjects as internal derangement of the knee joint, cervical rib, Dupuytren's contracture, and others. While one may sympathize with the Authors' dilemma in delineating the scope of this book, one would feel that this chapter is almost wholly a discussion of orthopedic conditions, not directly related to arthritis, or at least no more so than scores of other affections of orthopedic interest.

The book, however, represents a valuable contribution, and the editor and his associates deserve high praise.

P. C.

NUTRITION AND DIET IN HEALTH AND DISEASE. By JAMES S. MCLESTER, M.D., Prof. of Medicine, Univ. of Alabama. 5th ed. Pp. 800. Phila.: W. B. Saunders, 1949. Price, $9.00.

THE late world conflict and its associated dislocation stimulated a considerable volume of research in human nutrition. The results of much of this work have been published since the last edition of this book appeared 6 years ago. During the same period there have been significant studies of dietary factors in the macrocytic anemias, in cirrhosis and other diseases of the liver, in antibody formation, and in surgery and wound healing. Professor McLester has rewritten much of the book to bring it into line with the newer points of view or has incorporated new material in appropriate parts of the text. The chapters, Feeding of Infants by Professor Philip Jeans, and Nutrition in Industry by Dr. Robert S. Goodheart also have been rewritten. A new chapter, Feeding of Surgical Patients by Dr. Charles C. Lund, has been added. This edition compares well with earlier ones.

H. R.

NEW BOOKS

Help Yourself to Better Sight. By MARGARET DARST CORBETT. Pp. 218. New York: Prentice-Hall, 1949. Price, $2.50.

WRITTEN in support of the Bates system of improving vision by relaxing.

Headaches. By NOAH D. FABRICANT, M.D. Pp. 149. New York: Farrar, Straus, 1949. Price, $2.50.

THIS is as useful as such books for the layman can be in answering baffling questions where a visit to the physician is not needed, and in steering the patient to him when it is.

Fundamental Considerations in Anesthesia. By CHARLES L. BURSTEIN, M.D., Instructor in Anesthesia, New York Univ. College of Medicine. Pp. 153. New York: Macmillan, 1949. Price, $4.00.

IN this small book, the author has attempted to discuss many of the main problems that beset the anesthesiologist such as abnormalities of respiration; laryngeal spasm; physiological and pharmacological considerations of the patient in shock; celias plexus reflex; cardiac arrhythmia and gastro-intestinal autonomic reactions. Unfortunately, many of the statements that are made are undocumented and the discussions are too brief to be of real benefit. However, the subject matter should be thought provoking to the student of anesthesiology.

J. E.

George R. Minot Symposium on Hematology. Edited by WILLIAM DAMESHEK, M.D., and F. H. L. TAYLOR, Ph.D. Pp. 984. Illustrated. New York: Grune & Stratton, 1949. Price, $12.00.

Medical Clinics of North America. New York number, May, 1949. *Symposium on Cardiovascular Diseases, especially Hypertension.* Pp. 607-922. Phila.: W. B. Saunders, 1949. Price, $15.00 a year.

In this review the coverage of the practical aspects of hypertensive disease is at times incomplete in that some of the newer drugs have been omitted from the discussion on treatment. However, it is the Reviewer's opinion that the symposium is to be favorably recommended. It is useful in concisely presenting a discussion of the variable clinical course of hypertensive disease. This includes psychosomatic factors, role of the carotid sinus, organic vascular disease, management of the hypertensive disease of pregnancy, and the controversial subjects of capillary fragility and low sodium diet in clinical hypertension. The merits of various types of sympathectomies are discussed. C. C.

The Yearbook of Psychoanalysis. Edited by Sandor Lorand, M.D. Vol. IV. Pp. 356. New York: International Universities Press, 1949. Price, $7.50.

Twenty-two unrelated articles by as many authors, together with 2 pages of selected reading.

Psychosexual Development in Health and Disease. Edited by Paul H. Hoch, M.D., and Joseph Zubin, Ph.D., Columbia Univ. Pp. 283. New York: Grune & Stratton, 1949. Price, $4.50.

Your Child Makes Sense. By Edith Buxbaum, Ph.D. Foreword by Anna Freud. Pp. 204. New York: Internat'l Univ. Press, 1949. Price, $3.25.

Psychodiagnosis. By Saul Rosenzweig, Ph.D., Assoc. Prof., Psychology and Neuropsychiatry, Washington Univ., St. Louis, Mo., and Kate Levine Kogan, Ph.D. Pp. 380. New York: Grune & Stratton, 1949. Price, $5.00.

The psychodiagnostician relies in his work on tests which have been standardized. This book emphasizes the concrete materials and operations of the clinical psychologist rather than abstract principles of psychology. Illustrative case-histories are included. The book will be found to be both informative and useful. W. P.

NEW EDITIONS

Papers on Psychoanalysis. By Ernest Jones, M.D. 5th ed. Pp. 504. Balt.: Williams & Wilkins, 1949. Price, $8.50.

Hematology. By Willis M. Fowler, M.D., Prof. of Internal Medicine, Univ. of Iowa. With a Chapter by Elmer L. DeGowin, M.D. 2d ed. Pp. 535; 184 ills., 8 color plates. New York: P. B. Hoeber, 1949. Price, $8.50.

Among the advances recorded in this edition are: "The use of folic acid in various diseases, particularly sprue; the use of urethane in the treatment of leukemia and of nitrogen mustard in the lymphomas; the use of radiophosphorus in the treatment of polycythemia and leukemias . . ." DeGowin's completely revised chapter on Transfusion gives a good consideration of the Rh factor and other blood groups.

Fundamentals of Internal Medicine. By Wallace Mason Yater, M.D., Director, Yater Clinic; formerly Prof. of Medicine, Georgetown Univ., etc. 3d ed. Pp. 1451; 315 ills. New York: Appleton-Century-Crofts, 1949. Price, $12.00.

In these days when it is practically impossible for standard medical textbooks to keep up to date, this new edition through numerous corrections and additions successfully avoids congenital obsolescence. In general, it adheres to the author's original plan of presenting "the minimum amount of knowledge of clinical medicine a medical student or general practitioner should have." While such a text offers less to the post-graduate student or specialist, it probably has its place in teaching and seems to be liked by those for whom it is intended. H. Z.

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